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VOL. CLXXIX, No. 4 APRIL, 1930 No. 697

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THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES

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ESTABLISHED 1820

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THE

AMERICAN JOURNAL

OF THE MEDICAL SCIENCES

APRIL, 1930

ORIGINAL ARTICLES.

THE CLINICAL SYNDROME OF HYPERPARATHYROIDISM.

By David P. Barr, M.D.,

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Experimental Hyperparathyroidism. Following Collip's[1] discovery of an active parathyroid hormone, it became possible to study hyperparathyroidism experimentally. Collip[2] himself has summarized the effects of the injection of too much parathormone. The essential characteristic is hypercalcemia, sometimes exceeding 20 mg. per 100 cc. of serum. This develops rapidly, reaching a maximum in twelve to twenty-four hours, and falling as quickly as it arose. Symptomatically there is restlessness, respiratory distress, vomiting, diarrhea and, later, hematemesis and melena, collapse and death. There is usually hematuria, and in the fatal cases the kidneys cease to function about the time that the maximum value of hypercalcemia is attained. During this terminal period phosphates and nonprotein nitrogen of the blood rise rapidly; there is a decreased blood volume, thickening of the blood and a decrease in coagulation time which makes it difficult to obtain samples of blood for analysis. At autopsy there are hemorrhages into the kidneys and into the walls of the stomach and small intestines.

Almost immediately after Collip's preparation became available, Greenwald and Gross[3] studied the effects of toxic doses of parathormone. Giving to dogs amounts which caused death in about six days, they observed not only hypercalcemia but also a great increase in the excretion of calcium accompanied by an excretion of phosphorus that increased independently of the greater protein metabolism. Later

these same workers,[4] fearing that the changed excretion of phosphorus and calcium might be due to the severe intoxication rather than to a specific parathyroid effect, conducted a long-continued experiment in which parathormone was given daily for a period of almost two months. Under these circumstances, also, there was an increased excretion of phosphorus and calcium. The authors conclude that an abnormally high excretion can continue for a long period and that the calcium must be derived from bones, since no other tissue contains an amount sufficient to supply the 2.5 to 3 gm. of extra calcium which they found to be excreted during a fifty-five-day period.

Hueper[5] observed metastatic calcification in the lungs, kidneys, stomach, duodenum, heart muscle and, what is more surprising, in the thyroid gland. Accompanying these changes there were calcium casts in the tubules of the kidneys, multiple small hemorrhages in the brain, many thrombi in the small vessels of the myocardium with areas of localized necrosis and fragmentation of fibers. In one cat he found necrosis in the cortex of a suprarenal gland.[6]

Since the hypoparathyroidism of tetany is characterized by an increased tone and irritability of muscles, one might expect that hyperparathyroidism would be accompanied by the opposite condition of hypotonicity and diminished irritability. Collip[2] mentions the apathy of dogs which have received overdosage. Edward and Page,[7] who studied the effects of parathyroid extract on the heart, found incidentally that there was depression and in a few instances an "unmistakable atonia" of skeletal muscles. Berman,[8] using galvanic currents, demonstrated a definite decrease in the electrical response of the peroneal nerve of normal dogs after a moderate increase in serum calcium produced by parathyroid extract. Looney[9] was able to control muscular rigidity in patients with catatonic dementia precox by administering parathormone. In a series of eleven cases showing various degrees of rigidity he found a slight decrease in serum calcium. When the calcium in the serum was increased and maintained at a higher level with parathormone there was a decrease in muscle rigidity. Whereas before the injection it was impossible to open the patient's hands, afterward almost complete extension was obtained. It is of interest that Shohl[10] and his associates observed a diminishing electrical excitability in the muscles of a child who while suffering from infantile tetany was given small doses of parathormone. The improvement in the muscular condition roughly paralleled a return of the blood calcium to normal.

Hyperplasia of the Parathyroids. In man, as in many other animals, there is great variability in the number, location and size of the parathyroid glands. Mere size is not always a sufficient criterion to establish the presence of hyperplasia or hypertrophy. Cowdry[11] offers as average measurements 6 by 3 by 2 mm., with an average combined weight of 550 mg., but states that no two investigators ever give the same figures. Many German observers have used the range suggested by Biedl, who considered a length of 3 to 15 mm. and a breadth and thickness of 2 to 4 mm. as the limits of normal variation.

In the individual case, where enlargement is not great, it may be necessary to depend upon slight changes in the microscopic picture which, even in the hands of the best pathologists, offers great difficulties. It is quite possible, moreover, that in the parathyroid, as in

some other organs, functional dyscrasia may not always be reflected in recognizable anatomic changes. In spite of these difficulties, an undoubted hyperplasia of the parathyroids has been found, experimentally, under a great variety of conditions.

Erdheim,[14] in his monograph, described it in the spontaneous rickets of rats. Marine[15] found hyperplasia of the parathyroids of fowls on a low-calcium intake. Recently Higgins and Sheard[16] have found that enlargement of the parathyroids occur when either the longer or shorter waves of sunlight are deficient. Under these circumstances, the addition of cod-liver oil to the basic diet tends to maintain the glands at a more nearly normal size. They have also observed that after a few weeks of enlargement regressive changes with cyst formation may occur.

Susman[17] has produced enlargement of the parathyroids by repeated injection of guanidin, his evidence being based on microscopic examination. After extirpation of part of the parathyroids it has been shown that the remaining tissue undergoes hyperplasia or hypertrophy. This was shown to an unusual degree in experiments of Tanberg,[18] where all but one parathyroid gland was removed.

These experimental studies indicate an inherent power of the parathyroid glands to increase in size under a great variety of stimuli. Usually the enlargement is due to hyperplasia and not to hypertrophy of the individual cells.

In man, also, hyperplasia has been observed many times and under a great variety of circumstances. Sometimes it has been reported as hyperplasia or hypertrophy, but perhaps quite as often as tumor of the parathyroid. The dividing line between hyperplasia and tumor formation cannot always be sharply drawn. Ewing[19] has expressed it concisely: "In several cases," he says, "the hyperplasia has been regarded as adenomatous." The microscopic differentiation being very difficult, there is always a tendency in the literature to designate the condition as adenoma when one gland is much larger than the others, and to label it hyperplasia when several or all of the parathyroids are enlarged. It must also be remembered that there are in addition true benign tumors as well as a few which are highly malignant.

Incidence of Hyperplasia and Tumors. Parathyroid tumors have been recognized since Kocher,[20] in 1899, suggested such an origin for 5 glycogen-containing tumors which he had observed in the region of the thyroid gland. Whether or not these were truly of parathyroid origin, Kocher's report served to introduce the subject. Langhans[21] found 4 cases of similar character and De Quervain[22] reported 1. It is interesting that in these early tumors both thyroid and parathyroid tissue was found. On the other hand, De Santi's[23] tumor and Benjamin's[24] huge swelling (the size of a child's head) appeared to have a purely parathyroid structure. The case reports of tumors and striking hyperplasias have been collected from time to time. Among the many interesting reviews should be mentioned those of A. Kocher,[25] Bérard and Alamartine,[26] Harbitz[27] and especially the report of Hoffheinz,[28] who discussed all of the cases which he could find from 1900 (De Santi's case) to 1925. He was able to collect 45 cases in which parathyroid tumor or hyperplasia was certain and 15 others, the details of which were too incomplete to allow certain diagnosis.

In examining the literature, we have found a few cases which Hoffheinz omitted. In addition, several new cases have been reported in

the four years which have elapsed since he published his work. These have been summarized as follows:

Cases of Parathyroid Tumors. *Da Costa:*[29] A woman, aged thirty-two years, who had a mass in the neck which started at the age of twenty-three years following tonsillitis. Growth was painless, but attained the size of an orange. It was removed under the impression that it was an adenomatous goiter. The tumor was brownish-yellow and irregular. Sections showed parathyroid tissue. One year following operation a similar mass appeared on the opposite side. This was not removed for fear of tetany. No bone lesions or other accompanying pathologic changes were noted.

Bérard and Alamartine:[30] A woman, aged forty-three years, who had a tumor in the region of the left thyroid which had been growing for several months, causing dyspnea. In removing it, it was necessary to traverse 4 or 5 mm. of thyroid tissue. It was nodular and measured 20 by 15 mm. Microscopic examination revealed parathyroid tissue which was considered adenomatous. No mention was made of bone disease or other pathologic changes.

Roffo and Landivar:[31] A man, aged sixty years, with malignant tumor, arising in the region of the left lobe of the thyroid and metastasizing to the upper mediastinum. Examination following operation and later by autopsy, indicated a parathyroid origin.

Bergstrand:[32] A woman, aged fifty-seven years, who died of pneumonia. At autopsy she was found to have, in addition to pneumonia, an arteriosclerotic disease of the kidneys and a parathyroid tumor. Bergstrand found 10 other cases of severe nephritis in which there was hyperplasia of the parathyroids.

Hubbard and Wentworth:[33] A man, aged twenty years, with chronic interstitial nephritis, hydronephrosis, osteitis fibrosa of skull, ribs and vertebræ, with metastatic calcification of unusual degree in auricle, in arteries and about joints, but sparing liver, spleen, lungs, kidneys and stomach. Two parathyroid glands were about 2 cm. in diameter.

Bergstrand:[34] A woman, aged twenty-two years, who died suddenly after an unexplained illness. The thymus and two parathyroid glands were greatly enlarged.

Bergstrand:[34] A woman, aged fifty-eight years, who died following a hemiplegia. An enlarged thymus and two enlarged parathyroids were found at autopsy.

Fraenkel:[35] A case of ostitis fibrosa generalisata, with large parathyroid tumor.

Fasiani:[36] A woman, aged sixty-five years, who had always had a small mass in the right side of neck. For a short time she had noted a mass in the left side which grew rapidly until it attained the size of an adult fist. It was accompanied by severe pain. An attempt to remove it was unsuccessful, the patient dying on the table. The tumor had the structure of parathyroid tissue, was undoubtedly malignant and had invaded the thyroid gland.

Klemperer:[37] A woman, aged forty-nine years, who had a generalized carcinomatosis of bone from a primary tumor of the breast. Left inferior parathyroid measured 30 by 5 by 3 mm., was yellow and dense in consistency. Since the appearance was that of normal parathyroid gland, and the overgrowth was not limited to any one type of cell, it was considered to be a simple hyperplasia. In two areas of the parathyroid there were small nodules of metastasis from the primary tumor.

Looser:[38] A woman, aged fifty-one years, whose case was diagnosed ostitis fibrosa with cysts and brown tumors. At autopsy a tumor the size of a walnut was found back of the lower pole of the right lobe of the thyroid but separated from it. While it is probable that this was a parathyroid tumor, the description is not sufficiently complete to permit a certain diagnosis.

Dawson and Struthers:[39] A man, aged forty-nine years, who had a typical picture of ostitis fibrosa cystica with pathologic fractures. At autopsy five parathyroid glands were found. Four were normal or slightly enlarged; the fifth was the size of a walnut. Microscopically the appearance was that of a parathyroid adenoma.

Ferrero and Sacerdote:[40] A woman, aged sixty-five years, who had had a tumor in her neck for fourteen years. For three years she had noticed a tumor of the forehead. Operation on frontal region revealed an invasive malignant tumor which had the structure of parathyroid tissue and was diagnosed as a

malignant parathyroid tumor by the authors. No examination of the original tumor in the neck was reported. No changes in bones were found.

Kerl:[41] A woman, aged fifty-nine years, who, following childbirth at twenty-eight years, had developed symptoms of osteomalacia which was recognized and studied intermittently during the interval. At autopsy osteomalacia was apparent, but no cysts or tumors of the bones were described. All four parathyroids were said to be enlarged, measuring about 0.8 by 1 cm.

Kerl:[41] A woman, aged sixty-three years, who died of a cancer of the cystic duct. Twelve years before she had been diagnosed as a case of osteomalacia. At autopsy metastases from the primary tumor were found in the liver, the ovaries, the mesenteric lymph nodes and in the abdominal cavity. None were found in the bones. Parathyroids measured 10 by 6 by 4, 12 by 7 by 4, 25 by 5 by 3 and 11 by 5 by 4 mm. The condition of the bones was diagnosed as osteoporosis.

Gödl:[42] A woman, aged forty-two years, who was examined at autopsy following an operation for giant-cell sarcoma of the tibia. No other bone lesions were found. There were two tumors of the parathyroid, one 10 by 2 cm. and the other 5.4 cm. in diameter.

Nagelsbach:[43] A man, aged twenty-five years, with a tumor of the left upper parathyroid the size of a walnut, reported as pure hypertrophy. Accompanying this there was an extensive fibrous change of the entire skeleton.

Peneke:[44] A man, aged thirty-eight years, who died of a chronic nephritis. At autopsy contracted kidneys and metastatic calcification was found in the muscle of the left heart, in the smaller arteries, in the thyroid, kidneys and spleen. The great vessels remained free. There was also calcification in the apices of the lungs, in the skin and in the walls of the parathyroid tumor. Concretions were present in no other organs of internal secretion. The bones showed a picture of ostitis fibrosa.

Peneke:[44] A woman, aged fifty-nine years, who died of erysipelas. Diagnosed as ostitis fibrosa. The right lower parathyroid weighed 5 gm. The left lower, while not enlarged, showed the areas of proliferation described by Erdheim.

Perreira and Castro-Freire:[45] A young man, diagnosed as generalized fibrous ostitis, who had symptoms from the age of four years; a traumatic fracture at nine years; well-marked osteomalacia with cyst formation at sixteen years; death at eighteen years. At autopsy a parathyroid tumor was found. This was considered hyperplastic by the authors.

Herxheimer:[46] A man, aged thirty-two years, who showed at autopsy a mitral stenosis with calcium deposits in the heart muscle, in the aorta, the kidneys, lungs and wall of the spleen, but no calcification in the gastric mucosa. He had no pathologic changes in the bones. Three parathyroids were found. One was adenomatous and as large as a cherry.

Mandl:[47,45] A man, aged thirty-eight years, with severe generalized ostitis fibrosa cystica. At operation a parathyroid tumor measuring 25 by 15 by 12 mm. was found.

Guy:[49] A woman, aged twenty-nine years, who had had for six years a tumor of the neck in the region of the left lobe of the thyroid. The swelling was removed by operation. It measured 8 by 6 by 4 cm. and was diagnosed adenoma of the parathyroid. Ten months later the patient returned with three nodular swellings of the neck, interpreted by the author as compensatory hyperplasia of the remaining parathyroids. No bone changes were mentioned.

Allesandri:[50] A man, aged fifty-one years, with a tumor of the right humerus which followed an injury. Although there was no tumor in the region of the thyroid, the diagnosis of mixed thyroid and parathyroid adenocarcinoma was made from microscopical diagnosis of the tumor of the arm.

Gold:[51] A woman, aged fifty-four years, with generalized ostitis fibrosa cystica. At operation a parathyroid tumor measuring 25 by 16 mm. was found.

Beck:[52] A woman, aged forty-one years, diagnosed osteodystrophia generalisata, apparently typical of generalized ostitis fibrosa cystica. At operation two parathyroid tumors, one the size of a soft-shelled almond and the other the size of a coffee bean, were removed. The patient died of tetany.

Wilder:[53] A woman, aged thirty-two years, who had typical ostitis fibrosa. At operation a parathyroid tumor was removed.

Boyd, Milgram and Stearns:[54,55] A boy, aged ten years, with evidence of softening of the bones, diagnosed after clinical and Roentgen ray examinations

as generalized ostitis fibrosa. Operation revealed an adenoma of the left lower parathyroid.

Snapper:[56] A man, aged fifty-six years, with ostitis fibrosa cystica and an unusual degree of decalcification of bones. A parathyroid tumor was removed at operation.

Adding these 29 cases to those collected by Hoffheinz, a total of 74 examples of pathologically enlarged parathyroid glands may be considered. These include both malignant and benign tumors, as well as enlargements due to simple hyperplasia. Authentic malignant growths of the parathyroid glands are extremely rare, and it is a matter of interest that none of them has been associated with evidence of functional derangement of the parathyroids or with important conditions in the bones or elsewhere. The criteria for differentiating benign tumors from simple hyperplasia are ill defined. In some of the cases in which one is most tempted to diagnose tumors, there may be multiple growths. Guy's[49] patient returned ten months after operation with similar tumors in the region of the other parathyroid glands. Gödl's[42] patient had two large but quite separate parathyroid tumors. Such findings could be explained more simply on the basis of hyperplasia than of true tumor formation. All but about 17 of the parathyroid enlargements must, therefore, be considered to have resulted from hyperplasia.

Conditions Associated with Enlargement of the Parathyroid. Of the clinical conditions which have been reported in association with enlargement of the parathyroids, some appear to be incidental while others are found so frequently that they must be regarded as a possible cause or a possible result of the parathyroid changes.

Erdheim[12] described a case of parathyroid tumor in which acromegaly was present and in which a pituitary tumor was found at autopsy. Fine and Brown[57] mention a patient seen in Cushing's Clinic with acromegaly. In the third case of Molineus[58] there was found at autopsy a large tumor of the hypophysis with pressure atrophy of the surrounding bones. There was exophthalmos but no signs of acromegaly or any other functional disturbances of the pituitary gland were apparent.

In Herxheimer's[46] case the parathyroid enlargement was associated with mitral stenosis and cardiac decompensation. In one of Harbitz's[27] patients there was a generalized ichthyosis.

Possibly more significant are the cases associated with nephritis.

MacCallum's[59] patient, a young man, died in uremia following a nephritis, the symptoms of which had been apparent for several years. A parathyroid tumor was found at autopsy. He studied 2 other cases of advanced chronic nephritis and found in 1 abundant mitoses in the cells of the parathyroids. Bergstrand[32] saw 1 case of nephritis in which there was a small parathyroid tumor and 10 others in which the parathyroids were enlarged. Hubbard and Wentworth's[33] case of ostitis fibrosa had an advanced interstitial nephritis. Box and de Wesselow[60] saw a patient with nephritis in whom the serum calcium was elevated to 14.7 to 20.1 mg., a finding which was interpreted as possibly indicative of abnormal parathyroid function.

Still more striking and important is the association of many diseases of bones with hyperplasia or tumors of the parathyroid glands. In 45 cases collected by Hoffheinz, 27 had some disease of bone, while in the 29 patients whose records we have assembled, no less than 18 were so afflicted. Combining these figures, it appears that 60 per cent of

all cases of parathyroid enlargement have had evident bone lesions. If we exclude from the total number the 17 cases which may be considered either malignant or benign tumors, the association of osseous changes with parathyroid hyperplasia becomes even more impressive.

Of the 45 patients with diseased bones, 9 were diagnosed osteomalacia by the authors, 2 were thought to have rickets, 1 had general metastasis to bone from a mammary cancer; 1 had a localized giant-cell tumor of the tibia; 32 suffered from the generalized form of ostitis fibrosa cystica. In addition to these case reports, one should mention several more inclusive studies of the parathyroid glands in rickets and osteomalacia. Ritter[61] and, later, Pappenheimer and Minot[62] studied groups of children with rickets and compared them with children dying from other conditions. They found that the tendency to hyperplasia was general in rickets, thus establishing in children a fact which Erdheim[14] has already demonstrated in animals. In some instances the enlargement was slight, while in others the parathyroids were more than double the normal size. Thomas,[63] who studied the parathyroids in osteomalacia showed that in 6 out of 30 cases there was definite enlargement.

These observations leave no doubt that hyperplasia of parathyroid tissue is associated with many types of bone disease. Clinically the most frequent as well as the most striking association is with the generalized form of ostitis fibrosa cystica.

Generalized Ostitis Fibrosa Cystica (von Recklinghausen's Disease). In 1891 von Recklinghausen[64] published, in the volume commemorating Virchow's seventy-first birthday, a paper entitled "Ostitis, Osteomalacia and Osteoplastic Carcinomatosis." He also referred to a case reported several years earlier by Virchow.[65] Although there may be some doubt as to the proper classification of Virchow's case, there can be little question that the patient described by Hirschberg,[66] two years before the appearance of von Recklinghausen's paper, suffered from the generalized form of ostitis fibrosa cystica. Since that time occasional and scattered references to the disease have appeared in the literature. About 50 well-studied cases have accumulated and extensive reviews have been written by Dawson and Struthers,[39] Stenholm[67] and Mandl.[48]

The disease is more frequent in women and occurs usually in adult life. The age, however, is more variable. The cases of von Haberer,[69] Lissauer[70] and Bergmann[71] started in childhood, while Hart's[72] patient was an old man.

The cysts and tumors affect the long bones most frequently, but the jaw, pelvis and even the bones of the head (von Haberer[69]) may be involved. The swellings usually are not large, and when covered, as in the thigh, with heavy musculature, may not be recognized until a pathologic fracture calls attention to them. Fractures are extremely common, occurring most often in the femur and humerus. Pain accompanies the fractures, but in some cases seems to be an independent feature and, as in von Recklinghausen's original case, occurs in bones which are not known to be subject to fractures or injury.

Microscopically the swellings of the bones show hemorrhages which in some cases seem to dominate the picture. Barrie[73] designated his case as one of "hemorrhagic osteomyelitis." There is much fibrosis, and in many instances hemorrhage has been an obtrusive feature. Scattered in the fibrous tissue, a great number of giant cells may be found. The structure cannot be differentiated from that of the so-called giant-cell sarcoma of the type found in epulis.

The bone pathology is by no means limited to the cysts and tumors. In most cases there is a localized or general decalcification. This may be the predominant feature, as in Hart's case, which was called "osteomalacia with cysts and tumors." The frequency of the association may be judged from Morton's[74] review, where it is found that of 63 cases, 42 had either local or general softening and rarefaction of bone. Under these circumstances it might be thought and, indeed, has been stated, that ostitis fibrosa cystica is only a form of osteomalacia. Although the definition of osteomalacia is confused, the state most often so designated is associated with childbirth. Except during famine, it has occurred almost entirely in women. Ostitis fibrosa cystica, on the other hand, is not uncommon in men, and has no striking association with childbirth. Von Haberer[75] and Schmorl[76] consider that the softening of the bones in von Recklinghausen's disease has no relation either to puerperal osteomalacia on the one hand or to rickets on the other.

Von Recklinghausen did not recognize the parathyroid disturbance of the disease, and it was not until 1904 that Askanazy[77] found a parathyroid tumor in a woman with a disease which he called ostitis deformans without osteoid tissue, but which from the description may be considered ostitis fibrosa. Schmorl[78] reported a case of parathyroid hyperplasia in association with "osteomalacia and melanotic tumors," which was probably descriptive of the hemorrhagic cysts of von Recklinghausen's disease. Great impetus was given to the search by the excellent report of Molineus,[58] who saw 3 cases of typical generalized ostitis fibrosa, in all of which he found parathyroid tumors.

As has been stated, 32 cases have been found in which the two conditions have been associated. These, of course, do not include all of the cases of ostitis fibrosa cystica. In many of the earlier cases there was no examination of the parathyroids. This applies also to the more recent reports of Martland,[79] Crile,[80] Hartung[81] and Young and Cooperman.[82] But while in these instances the lack of association may be ascribed to failure to look for parathyroid change, there are some cases in the literature in which after meticulous examination no pathologic changes could be found. Stenholm[67] found 9 examples of typical and at times serious ostitis fibrosa, in none of which was there any evidence of pathologic change in the parathyroids. Because of this, the opinion has been expressed that while ostitis fibrosa cystica is frequently associated with parathyroid hyperplasia, it is not dependent upon it. Admitting this possibility, it must, nevertheless, be remembered that the recognition of parathyroid tissue is difficult, that it has a wide distribution from the thyroid cartilage to the areolar tissue of the pericardium, and that it may be embedded in the thymus, in the thyroid or even in the tongue. It is also conceivable that tissue which anatomically appears normal may have an increased or changed functional capacity. This possibility is generally recognized in the pathology of other glands of internal secretion.

Although anatomically the association of ostitis fibrosa and parathyroid disease had been recognized for twenty years, it was not until 1926 that Mandl[48] removed a parathyroid tumor by operation. It is significant and important in considering other cases which have been examined only by clinical means that he was unable to find any evidence of enlargement by palpation of the neck. The excised tumor,

however, measured 25 by 15 by 12 mm. Following the operation, there was a marked clinical improvement. The pains in the bones which had been excruciating before the removal of the tumor almost entirely disappeared. There was a gain in weight and increase in muscular power. Roentgen ray pictures showed slight but definite increase in the density of bones in which there had been previous decalcification.

Following Mandl's experiment, a number of similar cases have been subjected to operation for removal of parathyroid tumors.

The patients of Gold,[51] of Wilder[53] and of Boyd, Milgram and Stearns[55] were so greatly improved by the operation as to suggest complete arrest of the progress of the disease. Beck,[52] however, was not so fortunate, his patient dying of severe tetany twenty days after operation. Of the greatest significance is the case of Du Bois and Aub.[83] Operation was performed by Richardson[84] in the hope of discovering a parathyroid tumor. A most careful and painstaking search over the surface of both lobes of the thyroid revealed no abnormal growth. The removal of two normal-sized and microscopically normal parathyroid glands resulted, however, in great clinical improvement. Indeed, a completely bed-ridden invalid suffering from frequent pathologic fractures was enabled to leave his bed and carry on a useful occupation. This case, besides having an important bearing on the etiologic conceptions of the disease, substantiates the possibility already mentioned, that some of the cases of ostitis fibrosa cystica in which no parathyroid lesions were found may have had functional parathyroid derangement not discoverable by the method of examination. Of interest in this connection are the cases of Bauer,[85,86] Hohlbaum[87] and Strada,[88] which are mentioned by Hoffheinz but not included in his list of parathyroid tumors because, while the parathyroids were described as hyperplastic, the size was within the limits arbitrarily considered normal.

In addition to the changes in the bones and the association with parathyroid hyperplasia, ostitis fibrosa has a number of most interesting features. The calcium metabolism is extraordinarily disturbed.

Jacob and Schrott,[89] who were the first to investigate calcium relationships in the disease found an abnormally high excretion of calcium which they thought could be remedied by means of administration of calcium lactate. Mandl[48] found an increased excretion of calcium in the urine which was reduced to one-sixth of the original amount following the operation. Studies by Gold,[51] Wilder,[53] Boyd, Milgram and Stearns[55] have established an abnormal excretion of calcium in the urine as a constant feature of the disease which is remediable by operation.

The calcium content of the serum is greatly increased, as may be seen from the following table:

Author.	Highest calcium content of serum, mg. per cent.
Gold[51]	13.1
Wilder[53]	12.8
Boyd, Milgram and Stearns[55]	17.6
Du Bois and Aub[83]	16.5
Snapper[56]	23.6

Du Bois and Aub,[83] and also Boyd and his associates,[55] have found hypophosphatemia.

Calcium stones have been reported in the kidneys and ureters.

In 1884, seven years before von Recklinghausen's article, Davies-Colley[90] described a most interesting case of a girl brought up in a cellar, who developed a disease of her bones before the age of nine years. This was characterized by swellings in the jaw, ribs and pelvis, which were doubtfully considered calluses, but which may well have been due to multiple fibrocystic disease. In addition,

there were extensive calculi in the kidneys and ureters. A similar case without bone swellings was described more recently by Dereux.[91] Schönenberger[92] saw a case of undoubted ostitis fibrosa cystica in a woman with bladder disturbance and incontinence. The papillæ of the kidney showed small calcium infarcts. Gargele[93] described a patient who died of uremia and whose kidneys contained sand and stones that had resulted in hydronephrosis and pyelonephritis. Hoffheinz[28] found in his patient calcium infarcts as well as a large coral stone in the upper calyx of the right renal pelvis.

Most interesting metastatic calcification has been observed in a number of cases.

Hoffheinz, in addition to the changes in the kidneys, found calcium deposit in the lungs. Dawson and Struthers[39] found calcium infiltration of practically every organ in the body. This took the form of fine granules which in some instances became confluent masses. They were laid in the minute fibers of the elastic and connective tissue, in muscle fibers and also in epithelial cells. They were especially marked in the lungs, stomach and kidneys. No calculi were found. One of the most astounding examples of calcium deposit was recently reported by Peneke.[44] This patient died of chronic nephritis. At autopsy, calcification was found in the left heart, in the smaller arteries, the thyroid, kidneys, spleen, the skin and in the walls of the parathyroid tumor. The patient of Hubbard and Wentworth[33] had, in addition to ostitis fibrosa cystica, a fatal nephritis. The calcium deposits in the tissues were most extensive, but were found in the heart, the arteries and about the joints. The lungs, kidneys and gastric mucosa were spared.

Functional muscular changes have been noted in a number of cases.

Sometimes when violent pain has been a part of the picture, stiffness of the muscles has been described. Other cases, however, have shown an unusual flabbiness or weakness of the muscles. Dawson and Struthers studied the muscles of their patient without discovering any significant pathologic change. Hirschberg[66] and also von Recklinghausen[64] mentioned the wasting of muscles which admittedly may have been associated with disuse following injury. Hartung's[81] patient, however, had been diagnosed as a tabetic, although the reflexes were present. Barrie's[73] patient had persistent muscular weakness, much worse in winter. Four years before Barrie observed him he had been diagnosed amyotrophic lateral sclerosis. The case observed by Du Bois and Aub[83] showed muscular weakness. Electrical tests showed greatly diminished response to stimulation.

This discussion of generalized ostitis fibrosa cystica has not been concerned with a much more common condition designated in the literature as localized ostitis fibrosa cystica, solitary bone cyst or von Recklinghausen's disease. This occurs usually as a single cystic lesion in one bone and most often the femur, humerus or tibia. It is wont to affect young people below the age of twenty years and, although often extremely deforming, is accompanied by no deterioration of health. Pathologically the bone lesion cannot be distinguished from the cysts which have been described in generalized ostitis fibrosa. The relationship of these solitary cysts with giant-cell tumor on the one hand and with generalized ostitis fibrosa on the other has been much discussed and with little agreement. Reference may be made to the recent study of Geschickter and Copeland[68] on ostitis fibrosa and giant-cell tumor and to the article by Mandl,[43] who summarizes the evidence of the relationship between the localized and generalized form of ostitis fibrosa.

It is remarkable that, although the case reports of solitary cyst and of single benign giant-cell tumor have been much more numerous than

those of generalized von Recklinghausen's disease, we have been able to find only one, the case of Gödl,[42] in which there was an associated parathyroid enlargement.

Clinical Observations. A patient showing many of the features characteristic of ostitis fibrosa cystica has been observed by us during the past three years. Although her history was presented briefly in a previous publication,[94] her case is included in the present discussion in order that more complete data with pictures and exhibits may be presented and that the progress of the patient may be reported.

Case Reports. CASE I.—A woman, aged fifty-six years, entered Barnes Hospital, February 9, 1927, because of complete inability to walk, frequency of urination and a swelling of the right forefinger. She had been strong and healthy during her childhood. She married at the age of twenty-two years, but had never become pregnant. She lived with her husband on a small farm, where she worked hard. Some time in her girlhood she conceived a dislike for milk. She had other strong dislikes for food which finally led her to adopt a diet which was extremely ill-balanced. She was well, however, until the age of thirty-eight years, at which time she began to have frequency of urination and was told by her physician that she had an "inflammation of the bladder." For ten days she was in bed because of this disorder. The symptoms gradually cleared up and she remained well for nine years, until the age of forty-seven years, when pain and frequency of urination returned. After six months' treatment her physician told her that she had fibroids and that an operation was necessary. A hysterectomy and a partial oöphorectomy were performed. Following this operation she was never well. The urinary symptoms continued and she began to experience difficulty in walking, at first attributed to flatfoot, but later becoming so bad that she could get about only by supporting herself with her arms. She later noticed an increasing difficulty in lifting her feet from the floor. In February, 1926, from a rather trifling injury she fractured the right clavicle, which healed slowly.

In September, 1926, she injured the right index finger when the leaves of a table closed on it. A roentgenogram was taken of this finger and a diagnosis of syphilis was made by the physician. This alarmed the patient so much that she entered the hospital.

The examination revealed a remarkable degree of muscular hypotonia, most marked in the lower extremities. This seemed to apply both to the joints and to the muscles. The patient was able to go to sleep with her head on her ankles or with both ankles tucked under her head. She had a marked kyphosis; she was unable to walk and could not support herself. Electrical tests of the muscles showed little response to the faradic current. There was a fusiform swelling on the first phalanx of the right forefinger and a similar swelling on the right clavicle. A Roentgenogram of the bones of the skull and other parts showed irregular areas of rarefaction. The urine showed signs of moderate pyelitis. Flat plates of the kidneys revealed large collections of stones in the pelves. The right forefinger was removed. Examination by Dr. I. Y. Olch revealed a giant-cell tumor of the epulis type. Biopsy of the swelling on the clavicle showed normal callus formation.

After having been treated for her urinary symptoms for some weeks, the patient was sent home with the diagnosis of giant-cell sarcoma, bilateral nephrolithiasis and an unexplained hypotonia of muscles and joints.

She returned in February, 1928. She had been in an automobile accident and had fractured the left humerus. She had had a tooth removed from the upper jaw, and a tumor had formed in the maxilla. A biopsy of the ulnar swelling was suggestive of a benign giant-cell sarcoma, exactly similar to that removed from the right forefinger. No biopsy was obtained on the tumor of the jaw. It had the appearance of a cystic expansion of the maxilla. The teeth were loosened.

Roentgen rays of the skull and pelvis showed a greatly increased rarefaction. At the time of the first admission a punched-out area of rarefaction had been seen in the iliac bone. During the interval this had more than trebled in size. The

skull also showed the effects of a progressive decalcification. The legs which had previously been slightly bowed were definitely more deformed. An interesting change in the thumb which offered striking evidence of the softness of the bones occurred under observation in the hospital. Shortly after she came to us she was given occupational therapy which she undertook enthusiastically. As a part of this work, she had to press down with her thumb on each row of reeds before the next row was applied. This pressure resulted in deformity and bending of the terminal phalanx.

Unfortunately, calcium studies had not been made during the first admission. Examination of the blood now showed a calcium content of 16 mg. and a phosphate content of 1.4 mg. Repeated analyses under a variety of conditions gave a range of values from 12.4 to 16.6 for serum calcium and from 1.4 to 6 for phosphate.* Extensive metabolic studies revealed a constant negative calcium balance, with a loss of calcium in the urine which became greater as the calcium in the diet was increased.†

We were impressed with the similarity between the condition of this patient and that which had recently been produced by overdosage with parathyroid hormone. We were also stimulated by the reports of Mandl and Gold and by personal communication with Du Bois and Aub, whose case had been studied two years before. A reëxamination was made of the thyroid region without the discovery of a tumor. After repeated examination, however, a globular mass about the size of a small walnut was found embedded in the left lobe of the thyroid. Ordinarily, this rested beneath the clavicle and could be felt only when the patient swallowed.

Operation was performed by Dr. I. Y. Olch and a parathyroid tumor was removed together with a small portion of the left lobe of the thyroid. The tumor measured about 3 cm. in diameter. The central portion consisted of an irregular cyst which was surrounded by yellowish tissue. Microscopic sections revealed unmistakable parathyroid tissue which did not deviate significantly from the normal appearance of the parathyroid gland.

About two days after the operation the patient began to complain of slight tingling and numbness of the hands and a tightness and twitching of the corners of the mouth. At this time her serum calcium was still above the normal level. The following table gives in brief a record of the extraordinary picture which developed during the days following the removal of the parathyroid tumor.

In spite of large, even heroic doses of parathormone and of great amounts of calcium by mouth, the condition of the patient became steadily worse, until it appeared that she would die of tetany. Her life was apparently saved by the use of calcium chlorid intravenously. Following this period of acute symptoms, the patient gradually improved. It was not possible, however, to discontinue parathormone or the large doses of calcium.

During the first ten months following her operation she retained more than 300 gm. of calcium and was at all times in positive calcium balance. She developed no more tumors of the bones. Both the ulnar and the maxillary tumors decreased in size. The teeth which had been loose became tight in their sockets. Her muscular strength and tone improved rapidly for a period and then remained almost stationary and far below normal. Electrical tests showed the muscles to be more sensitive to the faradic current than they had been before operation. Frequent Roentgen ray pictures indicated a definite increase in the calcification of bones but not as great as might have been expected from the amount of calcium which she stored.

For several months she was watched in the hope that her increasing strength might enable her to bear her weight and to walk. Since this did not occur she was given massage, passive motion and physical reëducation. After weeks of this treatment she was able to walk for some distance holding onto a stretcher for support.

Her urinary symptoms showed no improvement; pain and frequency seemed to increase until they become almost unbearable. Examinations by Dr. D. K. Rose revealed that her bladder was of unusually small size with thick walls which went into spasm with slight irritation.

* This higher value was observed during a period of high phosphate feeding.

† The details of the metabolic studies on this and the following cases are being published in a separate report.[95]

FIG. 1.—Photograph of Case I, showing tumefaction of left maxilla, extreme flabbiness of muscles and abnormal mobility of joints.

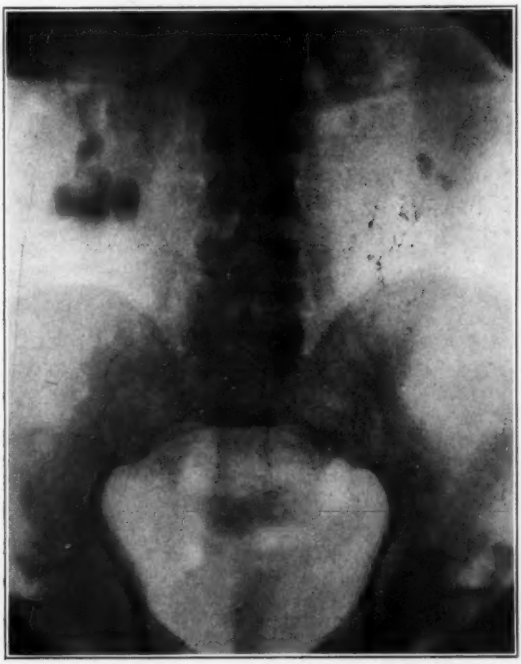

FIG. 2.—Roentgen ray of kidney region of Case I, showing bilateral nephrolithiasis.

FIG. 3.—Hands of Case I, showing irregularity of the outlines of phalanges and the giant-cell tumor of the first phalanx on the right hand.

FIG. 4.—Longitudinal section of amputated first phalanx in Case I, showing extent and character of giant-cell tumor.

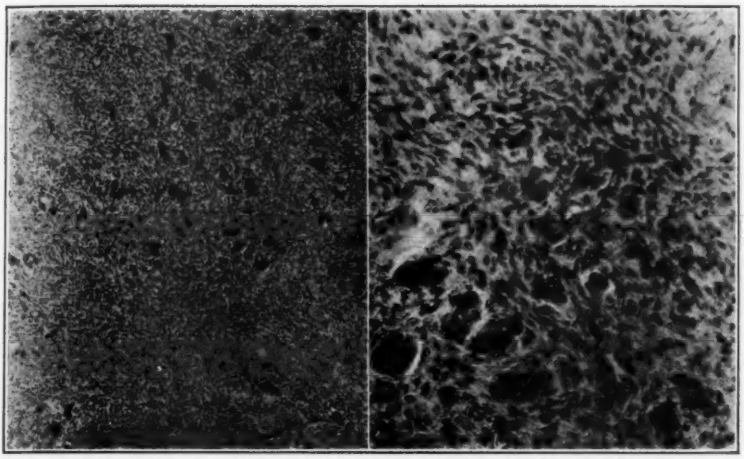

FIG. 5.—Microscopic appearance of giant-cell tumor of Case I. *A*, low power; *B*, high power.

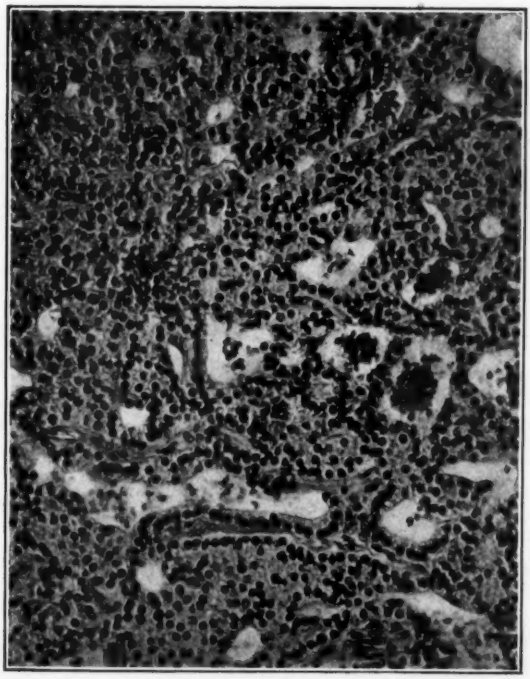

FIG. 6.—Microscopic appearance of parathyroid tumor of Case I.

FIG. 7.—View of left mandible and left maxilla, showing circular area of rarefaction at the roots of the left lower molars; the large area of rarefaction at the symphysis and another view of the tumor of the maxilla.

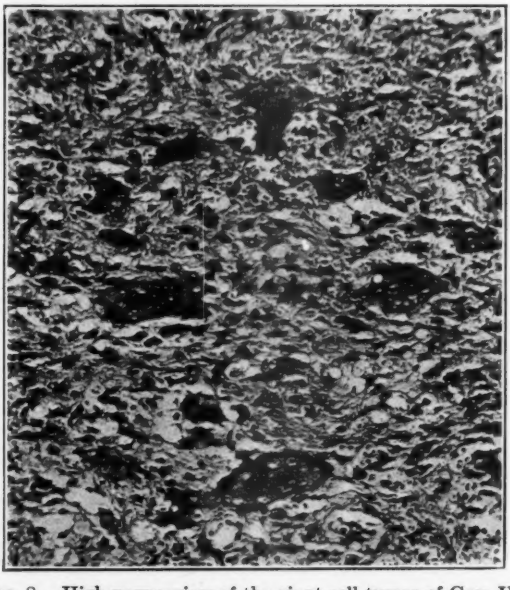

FIG. 8.—High-power view of the giant-cell tumor of Case II.

FIG. 9.—Spine of Case III, showing moth-eaten appearance of lower lumbar vertebræ and sacrum. To be compared with clear-cut outline of upper lumbar vertebræ.

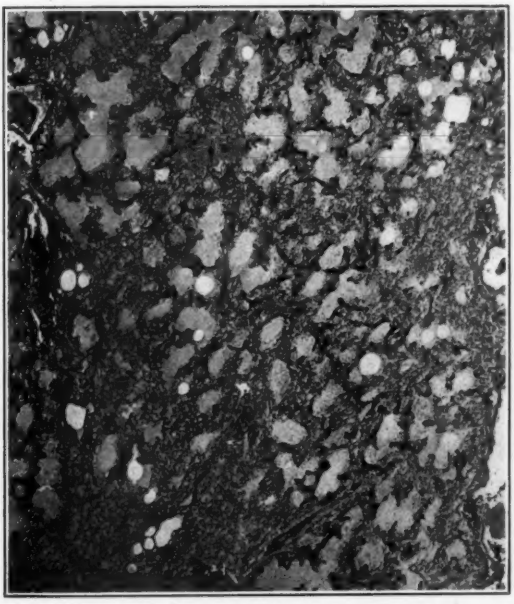

FIG. 10.—Metastatic calcification of the alveolar walls in the lungs of Case III.

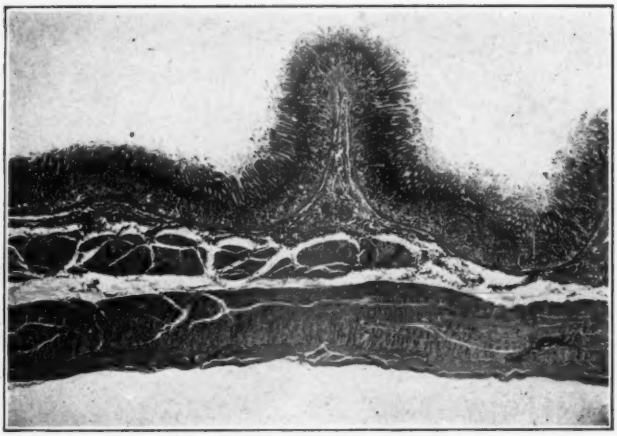

FIG. 11.—Metastatic calcification in the gastric mucosa of Case III, shown by line of dark-staining material in the lower portion of the glands.

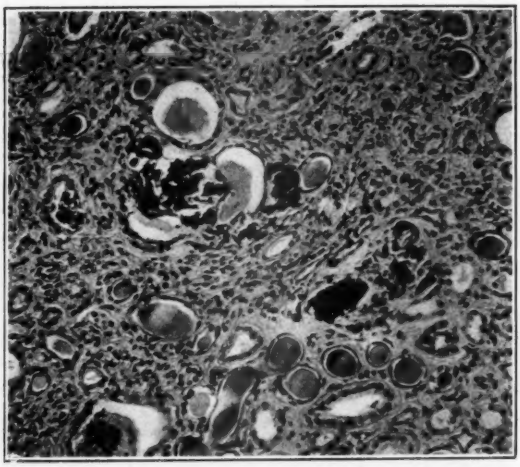

FIG. 12.—Metastatic calcification of kidney in Case III, showing calcium within the tubules and in the tissues surrounding them. The large patch of calcium in the right lower portion of the figure has completely replaced the tubule.

FIG. 13.—Femur of Case IV, showing multiple cysts.

FIG. 14.—Feet of Case IV, showing enlargement of second metatarsal of left foot.

FIG. 15.—Femur of Case V, showing cysts.

FIG. 16.—Tibia of Case V, showing cyst.

Day after operation.	Calcium in serum, mg. per cent.	Phosphorus in serum, mg. per cent.	Treatment.		Remarks concerning symptoms and treatment.
			Calcium lactate, gm.	Parathormone, units.	
Before	16.4	1.3			
Second	12.9	3.0			
Fourth	11.3	2.2	...	...	Beginning signs of tetany.
Seventh	10.8	5.2	...	...	Depression, vomiting, twitching of face, positive Chvostek; pains in legs.
Ninth	7.4	11.2	...	...	Increase in symptoms with spasm of larynx; nonprotein N., 33 mg. per cent.
Tenth	7.5	10.3	6		
Eleventh	...	...	12	...	Pains in muscles more severe; spontaneous muscle contractions.
Twelfth	7.5	3.0	10		
Fourteenth	...	...	6	25	
Fifteenth	6.5	3.4	18	35	Rapidly growing worse; signs of tetany less evident.
Sixteenth	4.1	3.2	12	75	Blood sugar, 135 mg. per cent
Seventeenth	...	...	18	50	Conditions grave; irrational.
Eighteenth	5.0	3.0	18	200	No objective signs of tetany; conditions grave.
Nineteenth	5.1	3.1	18	125	Nonprotein N., 31 mg. per cent
Twentieth	5.4	...	40	250	Condition about same; no signs of tetany; slight edema of ankles; B.P., 110/78.
Twenty-first	5.5	...	22	100	1.7 gm. calcium chlorid intravenously.
Twenty-second	7.5	3.7	18	50	Remarkable improvement overnight; 2 gm. calcium chlorid intravenously.

In July, 1929, she suddenly lost the power to move her legs. Deep reflexes had never been obtained and were not found after the paralysis. There was loss of superficial and deep sensibility and of the position sense. The muscles again became extremely flaccid. No sensory level, however, was discovered. Examination by Dr. S. I. Schwab failed to reveal a definite level of the lesion.

Roentgen ray of the spine showed, as before, a marked kyphosis. It was believed, therefore, that the cord had been subjected to pressure because of the abnormal position of the vertebræ. The use of a fracture board and some protection against weight bearing resulted in return of motion and sensation. Since this accident, however, she has not attempted to walk. She has lost some weight and there has been slight deterioration of her general condition. Recently she has shown an increasing infection of the bladder and renal pelves with impaired kidney function and nonprotein nitrogen retention of 50 mg.

This is considered to be a case of ostitis fibrosa cystica with bone cysts, giant-cell tumors of the epulis type, decalcification and softening of bone. It has the additional but also characteristic features of muscular hypotonia and nephrolithiasis, hypercalcemia, a tendency to excrete calcium in abnormally large amounts in the urine and hypophosphatemia.

Removal of a parathyroid tumor caused severe and almost fatal tetany, produced a hypocalcemia and a strongly positive calcium

Fig. 10.—Tibia of Case V, showing cyst.

Fig. 15.—Femur of Case V, showing cysts.

balance and hyperphosphatemia. It prevented any advance in the bone disease and resulted in some subjective and objective improvement.

The hypotonia exhibited by this patient is greater than has been previously reported. It seemed to involve the joints quite as much as the muscles. Furthermore, the ability of the patient to do contortionist tricks did not disappear with change in the muscles following operation. The patient gave a history of being unusually limber as a girl, and it is found that two members of her family are able to do modest contortionist stunts. Thus, while the muscular hypotonia and the lack of response to electrical stimulation were definite and striking features, they explain only in part the unusual mobility of the joints.

The development of tetany in this patient deserves special comment. It is by no means an isolated instance. Although Wilder's[53] patient did not develop actual tetany, she suffered three days after the operation from numbness and tingling of the fingers and toes which was relieved by calcium administered intravenously. Snapper's[56] patient had severe tetany with mania, relieved with difficulty by parathormone. Beck's[52] patient died with symptoms of tetany twenty days after operation. In this case, however, two parathyroid tumors were removed. It is interesting that in our patient the symptoms started while the serum calcium was above the usual normal level. They continued to increase while huge doses of parathormone were being given and while an abundance of calcium was being administered by mouth. At a time when her condition was becoming rapidly worse and hope for her recovery was all but lost, the intravenous injection of a comparatively small amount of calcium chlorid caused a most dramatic improvement. Although it was quite naturally assumed that the calcium taken by mouth had not been absorbed, later analysis showed that this was not true. In the entire period during which the tetany was developing, there was absorption of very large amounts of calcium. One can only conclude that calcium chlorid or the intravenous administration has some unexplained specific effect. This will be discussed in a paper on calcium metabolism in hyperparathyroidism. The successful use of intravenous calcium chlorid is emphasized here only because of its therapeutic importance.

Examination of the tissue removed at operation revealed only one parathyroid gland. Although it was expected that the remaining parathyroid tissue would be more than sufficient for the needs of the patient, acute tetany developed immediately, and now, after many months daily injections of parathormone are needed to prevent its recurrence. It can scarcely be assumed that this loss of parathyroid function is the result of postoperative adhesions or of injury of the blood supply of the remaining parathyroid tissue at the time of operation, since manipulation was limited to the left lobe of the thyroid gland and the right lobe was entirely undisturbed. The explanation is by no means clear. It seems possible that with the growth and hyperfunction of the parathyroid tumor, the remainder of the parathyroid tissue underwent a gradual but finally complete atrophy. It is also conceivable that there was a congenital absence of all but one parathyroid gland. In Erdheim's[96] first case of parathyroid tumor he found no other parathyroid tissue. Strauch[97] saw a patient with osteomalacia and

Günther[98] one with multiple giant-cell tumors, in both of whom a parathyroid tumor but no other parathyroid tissue was found.

Another possibility may be mentioned. During the state of hyperparathyroidism great amounts of calcium are removed from the bones, presumably because too great an amount of the parathyroid hormone is present in the body. Since with sudden removal of much parathyroid tissue the power of depositing calcium in the bone is restored, it might be assumed that calcium-hungry bones seize so much of the available calcium that other tissues and the blood are depleted and that tetany results. The events in the postoperative course of Snapper's patient furnishes some support for this explanation. The symptoms of tetany which developed shortly after the removal of the parathyroid tumor were extraordinarily severe. Recovery, however, was complete and during subsequent observation the patient exhibited no tendency to return to a state of tetany. In our own patient the explanation is not so completely satisfying. After fourteen months serious symptoms of tetany still develop whenever parathyroid and calcium are omitted in her treatment. The great amount of calcium absorbed during the period should presumably have satisfied any special avidity of the bones. It is fair to state, however, that the amount of parathormone necessary to maintain approximately normal calcium values is now somewhat less than during the first few months after operation.

Case II.—A farmer, aged thirty-eight years, entered Barnes Hospital, December 12, 1928, on the division of plastic surgery, complaining of a swelling of the jaw. The family history appeared quite unimportant. He had measles, mumps, whooping cough and pneumonia during childhood. He was well and strong until five years before admission, when following abdominal symptoms he was operated upon for gastric ulcer. Three years before admission, following a gastric hemorrhage, a second operation was performed for the same trouble. Thereafter he had little or no return of the gastric symptoms. His teeth had been in poor condition for years without any dental care. There was no history of dietary abnormality. He always liked milk and frequently drank as many as five glasses at a meal. There was nothing in the history suggestive of muscle hypotonia excepting an indefinite story of a short period about one year before admission, when he was "weak in his bones." Following his first abdominal operation he had had some nocturia; otherwise there were no urinary symptoms.

About eight months before the first admission to the hospital he noticed what he called a "gum boil" of the upper jaw on the left side. At no time was it painful. This gradually became larger. Three teeth at the site of the lesion became loose and were extracted by the patient himself with only slight local bleeding. A week before admission he had three severe hemorrhages from the gum.

The patient was well nourished and did not appear ill. His muscles were normally developed and of good tone. The heart, lungs and abdomen appeared normal. The blood pressure was 146 systolic and 80 diastolic. In place of the upper left canine and first and second bicuspid teeth, a tumor was present which extended into the hard palate and anteriorly beyond the alveolar margin. It was firm and not tender.

The urine showed no albumin or casts, no sugar and a varying specific gravity. The blood showed 4,600,000 red blood cells; 80 per cent hemoglobin and 14,500 white blood cells. The Wassermann and Kahn reactions were negative. The phenolsulphonephthalein excretion was 55 per cent in two hours.

Roentgen ray examination disclosed five tumors of the jaw. Near the one which had been recognized clinically there was an unerupted canine, and it was thought at first that the rarefaction of bone represented a dentigerous cyst. There was a large area of rarefaction extending from the lower incisor teeth to the symphysis menti; another was seen in the region of the right upper canine tooth. Tumors were also seen in both lower molar regions.

At two operations these were all removed by curette and cautery and treated with radium and deep radiation by Roentgen ray. Microscopic examination of the tissues removed at operation showed the tumors to be made up of cellular fibrous-tissue stroma in which there were vast numbers of large giant cells of the type seen in epulis.

About six weeks after the operations on the jaws the calcium and phosphorus content of the serum was studied for the first time. The serum calcium was found to range from 13.3 to 16.7 and serum phosphorus from 1.2 to 2.9 mg. per 100 cc. A more careful examination of the neck revealed a mass apparently about 1 inch in diameter, palpable just above the inner end of the left clavicle. This was elevated and more easily felt when the patient swallowed. The patient was then more completely studied as a case of hyperparathyroidism. There was still no evidence of hypotonicity of the muscles. Faradic stimulation of his muscles, however, required a somewhat stronger current than was needed by several normal persons used as controls. Roentgen ray of the urinary tract showed no evidence of stones. The urine displayed, at times, a slight trace of albumin and occasional casts.

During the interval of six weeks following operation he developed anemia. The blood showed: Red blood cells, 3,960,000; hemoglobin, 50 per cent; white blood cells, 8500; polymorphonuclears, 73 per cent; eosinophils, 1 per cent; lymphocytes, 23 per cent; large mononuclears, 3 per cent. It was felt that this might be the result of an unusually severe general effect of the radium treatment and perhaps to some extent related to the diffuse osteomyelitis of the jaws which had followed the operations.

Roentgen ray of the skull and the long bones of the body showed no other bone tumors and no osteoporosis.

Detailed studies of calcium metabolism showed a definitely negative balance, the excess excretion being chiefly in the urine. The urinary excretion was not greatly increased by a high-calcium intake, nor did this increase the serum calcium.

As there was little doubt as to the diagnosis of hyperparathyroidism, the tumor in the thyroid region was removed by Dr. J. B. Brown on June 18, 1929. It was found to extend beneath the clavicle and to be at least twice as large as was expected from the clinical examination. It was spherical and quite solid. The blood supply appeared to be from the inferior surface of the thyroid. Because of the apprehension caused by the almost fatal tetany which developed in our first patient, it was decided, upon the suggestion of Dr. Isaac Y. Olch, to transplant a small part of the mass into the rectus abdominalis muscle. A piece of a little less than 1 cm. in diameter was planted underneath the anterior sheath of the left rectus muscle. Microscopic examination of the tumor revealed normal parathyroid tissue with no evidence of malignancy.

Twenty hours after the operation the serum calcium had fallen to 10.6 and continued to fall until a minimum of 8.3 was reached on the eighth postoperative day. The serum phosphorus rose slightly to 3.6 mg. per 100 cc. During this time the patient had never experienced any definite tetany. At one time he had a little tingling about the face and in the fingers. Trousseau's and Chvostek's signs could never be elicited. At about the time the serum calcium was lowest he developed a slight diarrhea with some abdominal cramps lasting part of one day; otherwise he continually felt quite well. The calcium excretion in the urine fell promptly after the operation and became almost negligible, but there was little change in the calcium excretion in the stools. The calcium balance became positive, but there was no such marked tendency to store calcium as was noted with the first patient.

On August 12, 1929, two months after his operation, he returned for observation. The serum calcium was 10.5 and the serum phosphate 2.9 mg. per 100 cc. At this time he appeared to be quite well. He had been working hard and gaining weight. The lesions in his mouth had healed and Roentgen ray showed no evidence of any recurrence of the tumors. No mass could be felt under the scar, where a small part of the parathyroid tumor had been transplanted into the rectus muscle.

In this patient the history and the physical state indicate that the disease was of recent origin. The diagnosis of ostitis fibrosa must be made upon the occurrence of multiple giant-cell tumors which for some

reason were limited entirely to the upper and lower jaws. No decalcification or osteomalacic change was obvious in the examination of other bones. Clinical hyperparathyroidism was indicated by hypercalcemia and the abnormally high excretion of calcium in the urine. The muscular changes were slight and detectable only by means of electrical tests. The kidneys contained no demonstrable stones.

Following operation the serum calcium fell below the normal level and minor subjective symptoms of tetany developed. The course, however, is in striking contrast to the violent tetany which developed in the first patient. If in these cases an avidity of decalcified bones for calcium is to be regarded as an important factor in the production of postoperative tetany, its absence in this patient might be explained by the comparatively good state of the skeleton as revealed by Roentgen ray. The possibility must also be considered that the parathyroid tissue transplanted to the abdominal wall became sufficiently active to prevent the appearance of tetany.

It was unfortunate that the symptoms of hyperparathyroidism were not discovered earlier. The bone tumors were considered possibly malignant and the operations and subsequent radiation were correspondingly thorough. If hypercalcemia and the other evidence of parathyroid disturbance had been recognized before operation the possibility of malignancy of the tumors in the jaw would have been considered more remote and the effect of parathyroidectomy as a treatment for the bone tumors might have been tried. Although the result of such procedure cannot be predicted, the fact that the bone cysts of Case I decreased in size following parathyroidectomy suggest that considerable improvement might have resulted and that he might possibly have been spared serious and mutilating operations. The case illustrates the necessity of determining the values for serum calcium upon all patients presenting multiple bone tumors.

Case III.—A married German woman, aged forty-six years, entered Barnes Hospital, June 28, 1929, complaining of weakness, loss of weight, pain in her back. She was a private patient of Dr. J. J. Singer. The family history appeared quite irrelevant. At the age of ten years she had measles, and at fourteen years pneumonia. As a child there were frequent attacks of sore throat. She had occasional headaches. The patient was married at the age of twenty-two years and one year later her first child was born, being delivered by a midwife. Following this the patient did not do well. She failed to gain strength, and remained in rather poor health for the next four years. The symptoms at this time were indefinite, but were not suggestive of osteomalacia. At the age of twenty-eight years she had a second child. The puerperium was uneventful. She remained well until two years before her admission to Barnes Hospital, when she noticed severe and debilitating night sweats. Lassitude gradually became marked and she slowly lost weight. She had complained of an indefinite soreness in the left lumbar region and in the right shoulder. There was moderate nocturia but no other urinary symptoms. She was quite free from any pulmonary symptoms. For ten months prior to admission she had been treated by her local physician with ultraviolet light. This had given her a good tan color but had not increased her strength. She had lost weight from 135 to 90 pounds.

Examination showed a marked emaciation. There was no apparent pain or discomfort. The skin was warm, moist and elastic. A slight pallor of the mucous membranes was evident, but no cyanosis. The thorax showed nothing abnormal except the emaciation and rapid but regular heart. The abdomen was level with the costal margin. The soft edge of the slightly tender liver could be felt extending to the umbilicus. The spleen could not be felt. The

vertebræ were in good alignment and showed no abnormalities. There was no peripheral arteriosclerosis. Blood pressure was 115 systolic and 70 diastolic. There were no deformities or tumors of the long bones. The deep reflexes were hypoactive. Marked muscular atrophy was evident. The temperature was 39° ; respiration, 18.

The urine on admission was alkaline, of varying specific gravity and contained no albumin, sugar or casts. Blood showed: Red blood cells, 3,250,000; hemoblogin, 48 per cent; white blood cells, 6800; 48 per cent polymorphonuclears; 32 per cent lymphocytes; 2 per cent eosinophils; 6 per cent transitionals; 12 per cent large mononuclears. Wassermann, Kahn and Widal reactions were negative. Nonprotein nitrogen was 38 mg. Phenolsulphonephthalein, elimination, 51 per cent in two hours. Routine stool examination was negative.

The first part of the patient's course in the hospital was characterized by extreme weakness and emaciation which seemed to result from a remittent fever, ranging each day from normal to as high as 39° C. With these symptoms pulmonary tuberculosis was suspected, but repeated examination and Roentgen rays of the lungs were negative. Pain in the lumbar region and right shoulder and dull aching pains shooting down the legs from the knees to the ankles became more troublesome. There was, for a while, considerable pain and tenderness in the lower abdomen. This together with Roentgen ray findings suggesting a lesion in the cecum seemed to justify a diagnosis of tuberculosis of the cecum. Operation disclosed no abnormalities except the enlarged liver. Fever continued. She occasionally had headaches and vomited now and then. The emaciation was becoming extreme. She complained bitterly of pain in the lower back and left flank. Roentgen ray finally showed definite pin-point rarefaction throughout all the lumbar vertebræ and to a less extent in the pelvis, with rarefaction and a mottled lacy appearance of the bones but without much flattening of the vertebral bodies. Except for the ribs, no lesion of any other bones was demonstrated. There was no obvious osteoporosis of other bones. She was considered to have a neoplastic disease of bone. No Bence-Jones protein was ever found in the urine.

A study of the calcium and phosphorus of the blood was first made on October 5, 1928, when the disease of bone was first evident. The serum calcium was found to be 16 and phosphorus 3.7 mg. per 100 cc. By this time she had developed evidence of a fairly marked kidney insufficiency. Blood nonprotein nitrogen was about 70 mg. and phenolsulphonephthalein excretion was very low. Albumin and numerous hyalin and granular casts were found in the urine. With this there was an increasing hypotension, the systolic blood pressure averaging about 90.

The calcium and phosphorus metabolism was studied. On a calcium intake of about 0.5 gm. daily there was a definitely negative balance, with more calcium in the stools than was taken by mouth, and with an abnormal excretion of calcium in the urine considering the presence of a marked renal insufficiency.

A remarkable change in her general condition occurred during a period of eight days on a high calcium intake. The serum calcium rose to 17.8 mg. per 100 cc. and she became drowsy and irrational. During the latter part of this period she developed signs which were interpreted as cardiac failure; a marked tachycardia, dyspnea, râles at the lung bases and dependent edema. It seemed possible that this striking change was due to the influence of the high serum calcium on the nervous system and on the heart. Prompt lowering of the serum calcium seemed imperative. This was accomplished by the administration of neutral sodium orthophosphate by mouth and attended with obvious improvement. A few days later, however, she developed a bronchopneumonia from which she died on December 24, 1929.

At autopsy the muscles were found to be greatly atrophied. The whole body was extremely emaciated. There were fibrous-tissue adhesions about the operative scar on the abdomen, around the cecum and extending to the liver. In the lungs there were small areas of bronchopneumonia. The pleuræ were bound together in places by slight adhesions. Small stones were seen in the gall bladder and in the cystic duct. The thyroid was not enlarged but contained a few adenomata and a small cyst. On the posterior surface of the thyroid there were several large smooth bodies lighter in color than the thyroid tissue. Of six of these which were removed, three were found to be parathyroid glands.

The largest measured 11 by 5 mm. The vertebral bodies, ribs and clavicles were softened and cut easily with a chisel.

The chief interest of the autopsy attached to the microscopic findings. The parathyroid glands showed an essentially normal arrangement and structure. It was remarked, however, that the cytoplasm of the cells appeared swollen and vacuolated as though they were in active secretion. In one area of the gland there were larger cells with clear cytoplasm and nuclei.

The predominating type of cell in the bone marrow was large with a clear eccentric nucleus. The nucleolus was well definied and fine strands of stromata were condensed at the periphery, giving a typical cogwheel character to the nucleus. The cytoplasm was egg-shaped in most cases and the eccentric nucleus was placed near to one end. The appearance of these cells was considered typical of plasma cells. The changes were present in vertebræ, clavicles and ribs.

Metastatic calcification was found in the lungs, gastric mucosa and kidneys. In addition to areas of bronchopneumonia, there were in the lungs networks of blue staining material. Close examination revealed that this was calcium in the walls of the alveoli. In some places it extended in long straight lines as though following along bloodvessels, while in others it was accumulated in thick, dark irregular patches suggesting deposits with relation to bloodvessels. Sometimes it formed a ring around small capillaries which were filled with red blood cells. In the gastric mucosa there was a deposit of calcium which surrounded the base of gastric glands, forming a partial network about them. In other areas it clearly outlined the bloodvessels. In still other places it seemed to replace the cells of the gastric mucosa itself. These changes were limited to the distal portion of the gastric mucosa. Iron stains indicated the presence of iron in those areas where calcium was found.

The kidneys were involved in chronic degenerative change. The cortex was thin, with many scarred areas infiltrated with lymphocytes. Many glomeruli were completely fibrosed and hyalinized. Tubules were scarred and dilated and many of them were filled with hyalin casts. In some areas, especially in the pyramidal portion of the organ, deposits of calcium similar to those in the lungs and stomach were seen. Some formed a fine shell about the collecting tubules, while others extended into or replaced kidney cells. Some deposits outlined bloodvessels. In the cortex of the kidney such deposits were rare. As in the other organs, iron was found wherever abnormal calcium deposits had formed.

In this case, as in the others, there was hypercalcemia and an abnormal excretion of calcium in the urine. The metastatic calcification was in distribution and character in no way distinguishable from that which has been seen in von Recklinghausen's disease. The measurements of the parathyroid glands greatly exceeded the normal limits given by Cowdry.[11] If the normal range of Biedl[12] be accepted there might be some question concerning hyperplasia. Considering both clinical and pathologic data, however, there seems to be no doubt that hyperfunction of the parathyroids existed in this patient. The pathologic appearance of the bone marrow was characteristic of multiple myeloma of the plasma-cell type.

High values of serum calcium have been found in other cases of multiple myeloma. In Charlton's[99] patient it varied from 12 to 16 mg. Durman's[100] case had 16.1 mg. and Belden's[101] case, in which the diagnosis was not completely established, values ranged from 15.3 to 18.7 mg. Francis Smith[102] has recently studied 2 patients with multiple myeloma, both of whom had high serum calcium. In a patient whom we observed at the St. Louis City Hospital the serum calcium was 13.4 mg.

Metastatic calcification, while by no means constant in this condition, has been frequently observed. Permin,[103] Froboese[104] and others have shown calcium deposits in the kidneys. Austin[105] found them in the

lungs; Froboese in the uterine mucosa and Tschistowitsch and Kolessnikoff[106] in the ventricles.

The kidneys are seldom normal in multiple myeloma, although no constant renal picture has been associated with the disease. In this case it is possible that there was kidney insufficiency at the time the patient was first studied and that it may have influenced the calcium and phosphate content of the blood. In terminal nephritis, however, there is generally a tendency to hypocalcemia and to great increase in phosphate, conditions exactly opposite to those found in our patient.

The question of the relationship of nephritis to metastatic calcification is interesting. It is well known that abnormal deposits of calcium are found in the nephritis of mercury poisoning. In several patients exhibiting metastatic calcification in von Recklinghausen's disease there has been a coëxisting damage of the kidneys. This was true in the cases of Hoffheinz[28] and of Dawson and Struthers,[39] and particularly notable in the case of Hubbard and Wentworth.[33] It seems possible that metastatic calcification in ostitis fibrosa and in multiple myeloma may depend both on hypercalcemia and insufficient kidneys.

Bergstrand,[34] MacCallum[59] and others have found parathyroid hyperplasia in patients with chronic nephritis but with no bone disease. The possibility that some part or all of the parathyroid changes in this case are due to nephritis cannot be excluded.

Case IV.—A young woman, aged twenty-four years, entered Barnes Hospital because of a deformity resulting from an old pathologic fracture of the left femur. Her family history and past history were unimportant. She had always been quite healthy. When eleven years of age she fell while running and bruised her left knee. This resulted in little discomfort and symptoms had disappeared within a week. About three months later she began to have a constant dull pain in the left hip which was exaggerated by walking and did not entirely disappear when she was lying down. The pain continued while she was treated in various ways for flat feet. At the age of fourteen years she slipped, fell to the ground and suffered extreme pain in the left hip. Roentgen ray disclosed multiple cystic disease of the upper half of the femur with a pathologic fracture through the neck. At seventeen and again at eighteen years of age the pathologic areas in the femur were curetted and cauterized. She entered Barnes Hospital in October, 1928. Her general health had been good. There were no urinary symptoms; clinical and electrical tests of her muscles disclosed no hypotonicity. She had, at times, slight edema of the left ankle and foot, but none of the right. The general physical examination revealed no abnormalities. There was no anemia. The urine was negative and the Wassermann reactions were negative. Repeated careful examinations for a possible parathyroid tumor were negative. Roentgen ray showed cystic disease of the upper half of the left femur with the head in the acetabulum and the trochanter resting high against the ilium. Although Roentgen ray of the entire skeletal system disclosed no rarefaction, a spindle-shaped enlargement of the middle left metatarsal was found. During her stay in the hospital the head of the femur was resected and the trochanter was drawn down to the acetabulum. Tissue was taken for microscopic study, but was unsatisfactory. The diagnosis of ostitis fibrosa cystica was made.

For a period of four months complete studies of the calcium and phosphorus metabolism were made. The serum calcium ranged from 10.3 to 11.3 mg. per cent except in the two weeks following operation, when it fell as low as 8.5 mg. The serum phosphorus varied from 2.6 to 3.9 mg. Before operation the urinary calcium excretion was very low except on an exceedingly high calcium intake, when it mounted to about 500 mg. daily. There was a constant tendency to excrete excessive amounts in the stools. During a period of two months after her operation the calcium and phosphorus metabolism were quite normal.

CASE V.—A girl, aged eleven years, entered the St. Louis Children's Hospital because of a limp which had been present intermittently for seven years. She had always been quite well and strong and was very active. She was a healthy looking, well-nourished girl, showing no abnormality on physical examination except a slight outward bowing of the right thigh. There had never been any pain or tenderness of the right hip. Roentgen ray showed the upper half of the right femur to be greatly enlarged and to contain irregular cystic appearing areas. The midportion of the right tibia presented a similar area. A diagnosis of ostitis fibrosa was made. The urine was negative. There was a moderate leukopenia but no anemia. The serum calcium was 10.9; the serum phosphorus was 4 mg. per 100 cc.

In Cases IV and V the onset of the disease occurred in childhood. The Roentgen ray appearance of the bone was typical of ostitis fibrosa cystica, and since the symptoms were referred in each case to the femur only, it was thought at first that the patients were suffering from the localized form of the disease. The discovery of lesions in other bones in the metatarsal of Case IV and in the tibia of Case V indicated a condition which could not be sharply differentiated from generalized ostitis fibrosa. There was, however, no evidence of hyperparathyroidism. No tumor could be found in the thyroid region. The muscles exhibited no hypotonia; kidney stones were not apparent; the values for serum calcium were within normal limits and in Case IV extensive studies of the calcium excretion revealed no definite abnormalities.

Discussion. CLINICAL RECOGNITION OF HYPERPARATHYROIDISM. Several of the manifestations of experimental hyperparathyroidism are of a character which could be recognized if they occurred in the examination of a patient. Most of them, however, are not sufficiently distinguishing to be of crucial diagnostic importance. Kidney stones appear in many other conditions. Muscular weakness, diminished muscle tone or even a lowered excitability of muscles cannot be considered significant of any single malady. Increased urinary excretion of calcium might be a valuable diagnostic sign, but its study is always laborious and can be attempted only with special facilities. The level of blood calcium, on the other hand, is simply determined, and, although extensive studies have been made, hypercalcemia has been discovered in only a few conditions. In the consideration of our patients its presence was interpreted as evidence of an increased activity of the parathyroid glands. In the case of multiple myeloma it was the only clinical sign which suggested the possibility of parathyroid disease. It is important to inquire whether hypercalcemia may be considered as a pathognomonic sign of hyperparathyroidism.

Although it has been stated that calcium in the diet exerts an influence upon the level of serum calcium, the contention has not been established. Roe and Kahn[107] found that the ingestion of 5 gm. of calcium lactate by mouth caused hypercalcemia sometimes as high as 16 to 19 mg., the maximum change occurring from four to six hours after the ingestion. Bauer and Ropes[108] were unable to confirm this. Even with 10 gm. of calcium lactate they were never able to increase the calcium content of serum above 12.5 mg. Limited observations in our own clinic have shown no calcium figures higher than 13 mg. following the ingestion of calcium.

Hess[109] and others have demonstrated that experimentally the calcium content of serum may be artificially increased by the use of radiated

ergosterol. It has not been shown, however, that a comparable condition can occur spontaneously or can be recognized as a clinical entity.

Coates and Raiment[110] report values averaging 19 mg. per 100 cc. of serum in cases of gout. This has not been confirmed by Hench[111] and is questioned by Cameron.[112] Most interesting are the reports of hypercalcemia in arthritis deformans. Horwitz found values as high as 16.2 mg. in 5 of 14 cases. Mark[113] observed 4 cases in which values ranged from 13.3 to 20.3 mg. Nachlas,[114] however, was unable to find hypercalcemia in any one of 19 cases of osteoarthritis or in 18 cases of rheumatoid arthritis. Hench also failed to find this condition in 25 cases of infectious arthritis studied at the Mayo Clinic. Koenig and Bulger,[115] in our own clinic, were unable to find a single example of hypercalcemia in 82 determinations on 30 arthritic patients.

Recently Brown and Roth[116] have reported values for calcium ranging from 11.1 to 18.1 mg. in patients suffering from polycythemia vera. When phenylhydrazin was given and the number of red blood cells diminished the serum calcium was found to be lower.

While evidence concerning the occurrence of hypercalcemia in some of these conditions is conflicting, it is apparent that several diseases must be considered when high values of serum calcium are encountered. Joint diseases, polycythemia, abnormal ingestion of calcium or of irradiated ergosterol may, however, be recognized from examination and history and should cause little confusion in diagnosis.

The mechanism of the supposed hypercalcemia of gout and of arthritis and of the changes in polycythemia is not established. The work of Hess[109] indicates that radiated ergosterol does not cause high calcium values if the parathyroids have been removed. Except in the state following ingestion of large amounts of calcium, hyperparathyroidism may be considered as a possible cause of hypercalcemia in all of the conditions which have just been mentioned as well as in ostitis fibrosa, carcinomatous metastases in bone, multiple myeloma and nephritis—diseases in which parathyroid tumors or hyperplasia have been demonstrated.

The belief that the hypercalcemia of ostitis fibrosa cystica is due to hyperparathyroidism rests upon the fact that several of the accompanying symptoms: increased urinary excretion of calcium, abnormal deposit of calcium in tissues and muscle weakness are found in experimental overdosage with parathormone; upon the finding of parathyroid hyperplasia and tumors and upon the fall in serum calcium which accompanies the removal of a parathyroid tumor.

In multiple myeloma and in carcinomatous metastasis to bones the evidence is not so convincing. The parathyroid hyperplasia in our case of myeloma and the parathyroid tumor in Klemperer's[37] case of metastatic cancer indicate that the hypercalcemia observed clinically may have reflected increased function of the parathyroid glands.

From the evidence which has been presented, it appears that hypercalcemia should always arouse suspicion of hyperparathyroidism. It is, moreover, the only clinical sign which is of crucial diagnostic importance in the recognition of hyperparathyroidism, since a study of urinary calcium excretion is seldom feasible. Nephrolithiasis and hypotonia of

muscles must be considered important when they occur with hypercalcemia, but cannot be considered diagnostic when found alone.

It is possible that hyperparathyroidism may exist in the absence of hypercalcemia. The parathyroids are only one factor in the maintenance of the serum calcium level. The absence of vitamin D or of sunlight may be mentioned as causative in the low calcium values found in rickets. The recent work of Nitschke[117] indicates that the thymus and lymph nodes may be effective in lowering serum calcium. In nephritis the retention of phosphate is accompanied by hypocalcemia. In rickets both of animals and of children and in some cases of nephritis hyperplasia of the parathyroids has been demonstrated. This may represent a need for increased parathyroid function and may be secondary to factors having a tendency to reduce the level of serum calcium. Thus one could consider the serum calcium value in a case of rickets a resultant of two opposing factors, the absence of vitamin D tending to lower it while the enlarged parathyroids tend to raise it. Hyperparathyroidism, in the sense of increased functional activity might exist without hypercalcemia or, indeed, in the presence of low values of serum calcium.

Relation of Hyperparathyroidism to von Recklinghausen's Disease and Other Diseases of Bone. The question of the relationship of parathyroid changes to bone disease presents many difficulties. Erdheim, after studying the parathyroids in rickets, postulated that the hyperplasia of these glands is secondary to changes in the bone and acts as a compensatory or conservative process. This reasoning was applied to other conditions in which parathyroid and osseous changes were found to be associated. Mandl[48] attempted to test the theory. He removed the parathyroid glands from a man dying as a result of an accident and engrafted them in his patient with ostitis fibrosa cystica. If Erdheim's theory applied to this condition improvement should have resulted. Actually the patient became worse. Mandl then removed the parathyroid tumor, an operation which, as has been related, caused striking improvement in the symptoms of the disease. Quite naturally he concluded that his experiment disproved the application of Erdheim's theory to von Recklinghausen's disease.

One is tempted to go farther than Mandl and to state that ostitis fibrosa is secondary to hyperparathyroidism. Many of the symptoms which are identical with those of experimental parathyroid administration disappear after removal of parathyroid tissue. While cysts and giant-cell tumors of bone have not been demonstrated in experimental hyperparathyroidism, it might be assumed that these changes are incidental and follow injury in bones already softened by disease. The explanation receives some support from the frequent occurrence of hemorrhage in the cysts and from the pathologic studies of Looser, who suggests that the cysts and giant-cell tumors are the results of greenstick fractures in softened bone. One set of clinical observations seems to support the contention that the tumors are associated with parathyroid changes. Removal of the parathyroid tumor in Case I caused a regression in the size of the two cysts. No new tumors appeared, which is remarkable when it is remembered that at least two tumors had appeared during the year preceding her operation. In Case II no new swellings were detected after the parathyroid tumor was removed.

In the literature we have found no record of the appearance of cysts or tumors of the bones following parathyroidectomy.

Although the idea that the parathyroids may be entirely responsible for the changes of ostitis fibrosa is sufficiently alluring, it must not be accepted without reservation. It is significant that solitary cysts and single giant-cell tumors which are pathologically so similar to the multiple bone tumors of von Recklinghausen's disease, may exist without evidence of changes in the parathyroids. Moreover, in 2 of our cases (Case IV and V) there was multiple fibrocystic disease without hypercalcemia. In Case IV, which was thoroughly studied, there was no demonstrable disturbance in calcium metabolism. These cases demonstrate at least that similar pathologic changes may arise in bones from causes other than obvious hyperparathyroidism.

At the time our first patient came under observation the symptoms referable to increased parathyroid function were predominant. This was true also in the patients of Mandl, Gold, Du Bois and Wilder, and particularly in Snapper's case, in which all evidences of ostitis fibrosa had disappeared in an extraordinary degree of decalcification of the bones. But even in these cases, where parathyroid symptoms are most notable, it cannot be asserted that hyperparathyroidism is the primary factor in the disease. It is possible that bone changes occur first and stimulate the parathyroids to an increased activity which, in turn, aggravates the condition in the bones. If such an explanation is accepted, Cases IV and V of our series might be regarded as early stages of ostitis fibrosa cystica in which the secondary parathyroid changes had not yet become notable.

There seem to be no entirely valid reasons for deciding whether parathyroid hyperplasia is primary or secondary in ostitis fibrosa. In multiple myeloma, on the other hand, the probability is great that it is secondary to the bone changes. It cannot readily be assumed that a neoplastic process widely distributed through the body results from parathyroid hyperplasia. Neither can one believe that parathyroid changes were primary in Klemperer's case of carcinoma of the breast which metastasized to bone. The conditions seem comparable to those observed by Erdheim in rickets and by Thomas in osteomalacia. It is probable that many generalized diseases of bone, accompanied by extensive absorption or destruction of bone substance, lead eventually to significant parathyroid hyperplasia. In multiple myeloma, however, as in ostitis fibrosa, it may be possible for the hyperparathyroidism to become so active that it constitutes a menace in itself and assumes a predominant rôle in the clinical picture.

Summary. 1. The symptoms of clinical hyperparathyroidism are similar to those produced by the experimental injection of excessive amounts of parathormone. They include hypotonia and diminished electrical excitability of muscles, decalcification of bones, hypercalcemia and abnormal excretion of calcium in the urine. In some cases there is nephrolithiasis. Hypophosphatemia has been observed.

2. Hypercalcemia is the most significant clinical sign in the diagnosis of hyperparathyroidism. Although it may be found in a few other conditions, its presence usually indicates increased function of the parathyroid glands.

3. Hyperplasia of the parathyroids and clinical evidence of hyper-

parathyroidism have been found in many cases of generalized bone disease, including rickets, puerperal osteomalacia, multiple myeloma and carcinomatous metastases to bones. The parathyroid changes appear to be secondary to the changes in bone. While in some cases the increased function of the parathyroids may possibly serve a useful function, in other cases it becomes actually harmful by increasing the decalcification of the bones.

4. In generalized ostitis fibrosa cystica (von Recklinghausen's disease) the clinical picture of hyperparathyroidism is most frequently encountered. It may possibly be primary and is unquestionably harmful. In such cases removal of parathyroid tissue has accomplished clinical improvement and apparent arrest of the progress of the bone disease.

5. Determinations of the calcium and phosphate content of the serum should be made in all cases of generalized bone disease not only as a matter of interest but because of their therapeutic indications.

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HYPERTHYROIDISM AND PREGNANCY.*

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Hyperthyroidism and pregnancy in the same patient is a combination of great interest and importance to both surgeons and obstetricians. For many years it has been known that simple thyroid enlargement appears in many pregnancies. In goiter belts as high as 40 to 60 per cent of the pregnant women are known to have simple goiters,[9,16] and in nongoiter areas some thyroid enlargement during pregnancy is frequently noted. In this study, however, we do not wish to consider the incidence or importance of this type of simple goiter during pregnancy. We shall concern ourselves entirely with the study of hyperthyroidism as it complicates pregnancy, and of pregnancy as it is complicated by hyperthyroidism.

The objects of this study were to determine: (1) What the effect of hyperthyroidism is on pregnancy: Does pregnancy end disastrously when hyperthyroidism is present any more commonly than in normal women? (2) What effect has pregnancy on the course of hyperthyroidism? Does pregnancy increase or diminish the thyroid intoxication? (3) What effect has hyperthyroidism during pregnancy on the baby? Is congenital goiter or any other abnormality more common in babies born of thyrotoxic mothers? (4) What effect does pregnancy play in the causation of hyperthyroidism and what effect has pregnancy coming after thyroidectomy for hyperthyroidism in the recurrence of the hyperthyroidism?

For the first part of this study we have gone over the clinical records of all the thyroid patients treated in the Lahey Clinic from 1914 to August 1, 1929, and have selected all patients having both hyperthyroidism and pregnancy. Thirteen cases of exophthalmic goiter and pregnancy and 2 cases of secondary hyperthyroidism and pregnancy were found. In this interval there were 3678 toxic patients operated upon. Of this group 887 were adenomatous goiter with secondary hyperthyroidism and 2791 patients had primary hyperthyroidism. The incidence of pregnancy then in hyperthyroidism, in our experience, is 0.41 per cent. It is common knowledge that the incidence of hyperthyroidism in pregnancy is very low. Thus, there were no cases of hyperthyroidism in 937 obstetrical cases discussed by Yoakum.[9] At the Mayo Clinic[18] only 42 cases of pregnancy were found in 7228 cases of hyperthyroid-

* Read before the Boston Obstetrical Society, October 15, 1929.

ism (0.6 per cent). These figures clearly show the relative infrequency of hyperthyroidism in pregnancy. The fact that diminution of the menstrual function often accompanies thyroid toxicity and that the more severe the hyperthyroidism the less active is ovarian function, may well be related in some degree to the lack of fertility in thyrotoxic women.

In any discussion of hyperthyroidism during pregnancy a word of caution must be given as to the diagnosis of hyperthyroidism in pregnancy. It is known that during the later months of pregnancy the basal metabolism in a normal woman tends to rise to a relatively small degree (+25 to +30 per cent) above normal. This increased rate is not to be interpreted as evidence of hyperthyroidism but as due to the presence of an increased protoplasmic mass.[16,18,19,21] Before the diagnosis of hyperthyroidism can be made in any case, therefore, it is essential that in addition to a slight elevation in basal rate many positive symptoms and signs of the disease be present. We believe the metabolism must be elevated well above normal and probably above +30 per cent and a hyperplastic thyroid gland with tachycardia and definite activation should be present before a final diagnosis of hyperthyroidism in pregnancy can be safely established. It is very common to find tremor, nervousness and rapid heart in women, and when, in addition to these symptoms the enlarged thyroid gland of pregnancy is discovered, a diagnosis of hyperthyroidism may be too readily made.

What effect has hyperthyroidism on the course of pregnancy? Opinions on this point are not at all uniform, thus Gardiner-Hill[1] finds in a study of numerous statistics published in the literature that the results of pregnancy in exophthalmic goiter were very poor and 50 per cent of the cases ended in miscarriage or premature births. On the other hand, experience at the Mayo Clinic tends to show very definitely that no more abortions, miscarriages or premature births occur when the complication of hyperthyroidism is present than in normal women. Our experience coincides with this. We have found in our records 18 patients who had definite hyperthyroidism while pregnant. Sixteen of these women had primary hyperthyroidism (exophthalmic goiter) and 2 had adenomatous goiter with hyperthyroidism. Three of the 18 patients had thyroidectomies after their delivery, but were not operated upon while pregnant. Subtotal thyroidectomy was carried out in the remaining 15 cases of these women during their pregnancy and all the mothers recovered. One woman miscarried two days after a long ride home by automobile from the hospital. The miscarriage was eight days after her operation and her physician informs us that he saw no other cause for it than possibly the long ride. The 3 women not operated upon until after delivery had normal deliveries and later did well after thyroidectomy. We may conclude,

therefore, that hyperthyroidism does not cause a disastrous termination of the pregnancy in the majority of cases.

The second problem in this study, namely, what is the effect of pregnancy on hyperthyroidism, is not so readily answered. There are so many factors influencing every case of hyperthyroidism that it is always difficult to establish one as more significant than another in analyzing the end result. Furthermore, unless one has basal metablism studies with due allowance for the normal elevation in rate of late pregnancy, it is difficult to know what criterion can be accepted as to the effect of the pregnancy on the hyperthyroidism. H. Gardiner-Hill[1] and Hyman and Kessel[7] believe that there is no evidence that pregnancy makes thyrotoxic cases worse, but, on the contrary, that many cases improve during pregnancy and maintain their improvement afterward. L. Seitz[4] believed that pregnancy did not affect the hyperthyroidism in 40 per cent of his cases, but that in 60 per cent the hyperthyroidism was made much worse by the pregnancy. Mussey, Plummer and Boothby[18] do not find that pregnancy makes the course of hyperthyroidism any more difficult to handle or influence it to any degree. We have not seen anything occur in any woman with hyperthyroidism and pregnancy which does not commonly occur in nonpregnant thyroid cases of that type. Multiple-stage thyroidectomies have been just as necessary in pregnant as in nonpregnant women, but no more so (20 per cent had multiple-stage operations). We believe, however, that pregnancy during hyperthyroidism is certainly a very definite added load for the patient to endure whether or not it affects the degree of hyperthyroidism which is present. Pregnancy must increase the patient's muscular work and add to the metabolic requirements. It is our daily experience that thyrotoxic patients cannot tolerate additional loads, and we feel certain that from this point of view, at least, pregnancy is a serious burden in all severe thyroid intoxications.

The third problem that we hoped to answer in this study was what effect hyperthyroidism during pregnancy would have on the baby. In all our cases of hyperthyroidism which went to term and had living babies, all the babies were normal. There were in this group no congenital defects, no goiters and no evidence of insufficient thyroid function, that we were able to trace through either the mothers or their physicians. We have not discovered in these cases any evidence which even suggests that a baby born of a thyrotoxic mother will be abnormal in any way.

The possibility that pregnancy is related to the occurrence of hyperthyroidism has frequently been suggested. The fact that pregnancy is so commonly accompanied by some thyroid enlargement has doubtless given strength to this suggestion. Any proof of this theory, however, is necessarily difficult, and statistical studies, unless very striking, may well be misleading. We have, therefore,

gone over the histories of 602 consecutive patients with hyperthyroidism and attempted to learn something of the relationship between the occurrence of pregnancy and the onset of hyperthyroidism.

It was necessary to exclude certain of these 602 cases from this study. Thus 85 were males; 14 were under eighteen years of age; 155 were married and over the childbearing age; 49 were single and over thirty-five years of age; 7 records were unsatisfactory. There were, therefore, 292 cases to whom letters could be sent and who could be investigated. Of these, 203 replied to our inquiries. These 203 replies from women of childbearing age form, therefore, the basis of this section of our study of the relation between pregnancy and the onset of hyperthyroidism.

In this group there were 41 women who stated that the onset of their hyperthyroidism was dated within three months of delivery. That is to say, of the 510 women of the large group, 41, or 8 per cent, said their pregnancy and their hyperthyroidism occurred within three months of each other and might be related. If we consider only the 347 women in the group who were married, however, it would be true that roughly 12 per cent of the married women had been pregnant within three months of the onset of their hyperthyroidism. This is not, in our opinion, such an outstanding or remarkably striking relationship that it will permit any deductions that pregnancy was or was not a factor in the onset of the hyperthyroidism.

Our figures tend to prove that there were, if anything, fewer pregnancies before the onset of hyperthyroidism in this group than are to be expected in any ordinary group of women: 118 of the 203 women who answered our inquiries were married and under forty years of age; 90 of these women had had at least one pregnancy before the onset of their hyperthyroidism. If it be admitted that 10 per cent of all marriages are childless it is seen that 90 pregnancies in 118 women is definitely below the normal expectation. We believe that these findings tend to prove that pregnancy cannot be considered an etiologic factor in hyperthyroidism.

Our belief that pregnancy is not a factor in exciting hyperthyroidism is further borne out by our study of pregnancy occurring after thyroidectomy for exophthalmic goiter. Fifty-three of the 203 women bore 69 children after thyroidectomy and only in 1 case was there even a question of any recurrence of thyrotoxic symptoms during the pregnancy and puerperium. In this 1 case the physician reported that he suspected some return of thyroid toxicity but had been able to control it completely with Lugol's solution. Such a case may or may not be a recurrence of hyperthyroidism during pregnancy. At any rate, the fact that 69 pregnancies failed to produce any serious return of hyperthyroidism in any one of 53 postoperative hyperthyroidism patients is, in our opinion, very

excellent evidence that pregnancy is not a potent factor in the etiology of hyperthyroidism.

The results of the 69 pregnancies are also known: 47 of the babies had been born normally and were healthy children; 8 babies were unborn at the time of our study and 14 of the babies failed to live from either miscarriage, abortion or disease of the newborn. In 13 of these cases there was no relationship between the previous thyroid disease or operation and the fetal death. In 1 case the cause of fetal death was unknown. The loss of 14 babies in 69 pregnancies is a mortality of 20 per cent. This figure is certainly within the normal expectation of abortion or miscarriage in pregnancy among a group of normal women. In fact, many obstetricians recognize a much higher figure as much more probable among all types of women. We, therefore, feel that subtotal thyroidectomy for hyperthyroidism does not render future pregnancy unusually dangerous to the baby.

Seven of the women in this particular group of cases were pregnant at the time that thyroidectomy was performed. All the mothers recovered and all the pregnancies terminated normally save in 1 case, which ended in a miscarriage about two weeks after the thyroidectomy. No cause for this miscarriage could be determined and we cannot say that it was or was not related to the thyroidectomy. This group of 7 cases gives us reason to believe that thyroidectomy for exophthalmic goiter can be undertaken during pregnancy with safety to both mother and child if the usual safeguards of thyroid surgery are carefully maintained.

Conclusions. 1. In this Clinic the incidence of pregnancy in 3678 cases of hyperthyroidism was 0.41 per cent.

2. Special care is needed that the normal elevation of metabolism in late pregnancy is not interpreted as evidence of thyroid disease.

3. Hyperthyroidism does not cause an unnatural termination of the pregnancy in the majority of cases when it is properly treated.

4. We believe that pregnancy does not increase the toxicity of primary hyperthyroidism except as the increased proplasmic mass of pregnancy brings some increase in metabolism. Pregnancy is, however, distinctly an added burden in hyperthyroidism, which should be avoided if possible.

5. Babies born of thyrotoxic mothers are not abnormal.

6. Pregnancy does not appear to be a cause of primary hyperthyroidism.

7. Pregnancy after thyroidectomy for primary hyperthyroidism does not cause recurrence of thyroid toxicity.

8. Babies born of mothers who have had thyroidectomy for hyperthyroidism are normal.

9. Thyroidectomy for primary hyperthyroidism can be undertaken during pregnancy with safety to both mother and child.

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THE EFFECT OF INSULIN ON PATHOLOGIC GLYCOGEN DEPOSITS IN DIABETES MELLITUS.

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Introduction. Since Ehrlich,[1] in 1883, found in 14 cases of diabetes the peculiar glycogenic infiltration of the epithelium of Henle's loops in the kidneys, this lesion has been regarded as the most definite anatomic finding in active diabetes mellitus. Other less constant abnormal glycogenic deposits associated with the disease were also noted by Ehrlich: the increased glycogen in the heart muscle fibers; glycogenic granules in the leukocytes; and large glycogen-filled vacuoles in the liver cells. Curiously enough, it was not until twenty-three years later that Meixner,[2] soon followed by Best,[3] demonstrated the glycogen-filled vacuoles in the epithelial cells of the liver to be the nuclei.

It is hardly fair to say that glycogenic infiltration of the epithelium of Henle's loops is definite evidence of diabetes mellitus, as glycosuria, from any cause, gives rise to this change. Thus Gierke[4] states it has been found: (1) in diabetes mellitus; (2) after experimental extirpation of the pancreas; (3) after extirpation of the celiac plexus; (4) in phloridzin poisoning.

In the first 3 instances the blood-sugar level is increased, in the last it is normal, or low. The one point in common is the presence of glucose in the urine.

Since, in the great majority of cases, glycosuria in the human means diabetes, the presence of glycogen in Henle's loops may be interpreted as an indication of active diabetes.

It is rather interesting that Ohohashi[5] finds that the distribution of glycogen in the diabetic kidney is exactly the same as that in the normal kidney of the anura. In normal frogs he found traces of glycogen even in the leukocytes. He also mentions that glycogen occurs in the epithelium of the pancreatic ducts in mammalian fetuses. I have found it in this location in several cases of diabetes.

Loeschke[6] gives the following table based on 6 cases of diabetes, showing the glycogen present elsewhere in the kidneys besides Henle's loops:

TABLE I.—AMOUNT OF GLYCOGEN IN RENAL EPITHELIUM (LOESCHKE).

Case.	Glomeruli.	Convoluted tubules.	Henle's loops.
I	+++	+++	++
II	++	+	+++
III	+	+	++
IV	−	+	++++
V	−	−	+
VI	−	−	+

Rosenberg[7] also mentions a case in which glycogen was present in the glomeruli and epithelium of the convoluted tubules, as well as in Henle's loops. In certain of the cases summarized in this paper, I have found a similar distribution of the glycogen. Sandmeyer[8] gives a quantitative determination of the glycogen present in the kidney of a girl, aged nine years, who had had diabetes for two years, 0.1158 gm. per 100 gm. of kidney substances. The liver contained 0.6130 gm. per 100 gm., or nearly six times as much.

Since pathologists have considered for years that one of the most constant signs of diabetes is the occurrence of glycogen in the epithelium of Henle's loops, it was somewhat disconcerting to me to find in undoubted cases of diabetes mellitus no evidence of abnormal glycogen deposits. In some of these cases glycogen was present in the liver cell nuclei, but it has long been known that there are many conditions other than diabetes in which there is this intranuclear deposit of glycogen. In fact, approximately one-third of all post-mortem examinations show this deposit to a greater or less degree.[9,10]

Methods. While Best's carmine stain probably is not entirely specific for glycogen, it is none the less the most satisfactory method available for demonstrating this substance. Tissue from surgical specimens or from autopsies is fixed in absolute alcohol and celloidin sections are cut and stained by the Best technique given by Mallory and Wright.[11] As controls, sections placed in saliva for ten minutes

were also stained. In certain cases the iodin method of Langhans was also used.

In renal epithelium and liver-cell nuclei the presence of vacuolization as shown in paraffin sections with various stains is a further aid. This vacuolization runs closely parallel with the glycogen content as shown by Best's stain in tissues fixed under one hour postmortem, and is much more marked than the carmine stain would indicate in tissues fixed a longer time postmortem.

In most tissues there is a rapid drop in demonstrable glycogen in the first hour after death, and but little change for some hours thereafter. Yater, Osterberg, and Hefke[12] found by microchemical analysis that one-half to three-fourths the glycogen in the rabbit disappears in the first hour, and that from then on the rate of decrease is slow.

Results. Both surgical and postmortem material has been utilized, and the glycogen distribution studied in the various tissues, particularly heart, liver, kidneys, pancreas, voluntary muscle and skin. Both insulin treated cases of diabetes and cases not treated with insulin are included, as well as a control series of nondiabetics.

Heart. Glycogenic infiltration of the heart muscle is marked in many cases of diabetes. It is particularly striking in those fibers at the margins of infarcts. It can also be found there longer postmortem. Whether this means greater storage of glycogen or that the fibers are damaged and so deficient in glycogenolytic ferment is somewhat difficult to decide. On the basis of tissue fixed under thirty minutes postmortem an abnormally large storage of glycogen seems the more likely.

So far as the amount of glycogen in the muscle as a whole is concerned, there is but little difference between the insulin treated cases of diabetes and the control series. The diabetic cases not treated with insulin show a high proportion of heavy deposits of glycogen.

TABLE II.—GLYCOGEN CONTENT OF HEART.

Type of treatment.	None.	Slight.	Moderate.	Marked.
No insulin	..	5	3	5
Insulin	..	1	..	1
Insulin, infection present	..	3	7	4
Control (nondiabetics)	2	4	11	3

Liver. Since glycogenic distention of the nuclei of liver cells is found in many other conditions than diabetes, this cannot be regarded as of particular importance. However, in diabetic patients there is a very definite reciprocal relationship between the amount of intranuclear and the amount of intracytoplasmic glycogen. When intranuclear glycogen deposition is marked, there is but

little or even no glycogen in the liver cells in these cases. Conversely, when there is much glycogen stored in the cytoplasm, there are few or no nuclei containing it.

TABLE III.—LIVER CELL NUCLEI.

Type of treatment.	None.	Slight.	Moderate.	Marked.
No insulin	1	8	5	7
Insulin	7	5	1	..
Insulin, infection present	3	8	7	4
Control (nondiabetics)	10	6	3	1

Glycogen is most marked in those cells in the periportal region. Frequently the cells about the central vein contain none, although it is present elsewhere in the lobule in large amounts. There is no antagonism between the deposition of fat and glycogen, both being often present in the same cells in large amounts.

TABLE IV.—GLYCOGEN CONTENT OF LIVER CELLS.

Type of treatment.	None.	Slight.	Moderate.	Marked.
No insulin	4	4	5	1
Insulin	..	..	1	2
Insulin, infection present	2	6	3	5
Control (nondiabetics) .	..	9	9	4

The above table gives indisputable evidence of the effect of insulin in promoting the deposit of glycogen in the liver, although this effect is somewhat lessened in septic cases.

Pancreas. In 8 instances considerable amounts of glycogen and in 10 instances slight amounts were found in the epithelium of the pancreatic ducts, both the smaller ducts with cuboidal epithelium and the larger ducts with columnar. As has already been mentioned Ohohashi[5] found this distribution in mammalian fetuses. I have encountered glycogen nowhere else in the pancreas.

TABLE V.—GLYCOGEN CONTENT OF PANCREATIC DUCT CELLS.

Type of treatment.	None.	Slight.	Moderate.	Marked.
No insulin	4	5	3	2
Insulin	4	..	..	..
Insulin, infection present	11	5	3	..
Control (nondiabetics)	22	.	..	..

Kidneys. Insulin treatment definitely reduces the amount of glycogen present in the kidneys. In many cases it is entirely absent. In many others it is considerably reduced over that found in cases of diabetes not treated with insulin. Although Henle's loops are the most typical loci for glycogenic infiltration, the convoluted tubules as well are occasionally involved. Glycogenic

granules may even be demonstrated within the capsular space, but these probably are artefacts due to postmortem diffusion.

TABLE VI.—GLYCOGEN CONTENT OF KIDNEY.

Type of treatment.	None.	Slight.	Moderate.	Marked.
No insulin	3	7	3	16
Insulin	6	3	..	1
Insulin, infection present	1	12	6	3
Control (nondiabetics)	15	1	..	..

Voluntary Muscle. Many specimens of muscle came from legs amputated for gangrene. They, therefore, may possibly be of dubious value owing to the influence of an impaired circulation, which would certainly interfere with normal cellular function, and might well influence the function of glycogen storage. However, the muscle was always taken from as near the site of amputation as possible. In the autopsy material, portions of the pectoralis major were utilized.

There is an apparent tendency for decrease in muscle glycogen in the cases of diabetes

TABLE VII.—GLYCOGEN CONTENT OF VOLUNTARY MUSCLE.

Type of treatment.	None.	Slight.	Moderate.	Marked.
No insulin	..	1	3	1
Insulin	..	..	1	..
Insulin, infection present	1	13	11	6
Control (nondiabetics)	..	7	12	8

Skin. Unna[13] has recently called attention to the large amount of glycogen in normal skin. Before learning of his work, I had found large amounts of glycogen in the skin of normal individuals, and lesser amounts in the skin of diabetics. The epithelium of the stratum corneum, sweat glands, sebaceous glands and follicles are heavily loaded. Becker[14] speaks of much glycogen in the duct cells of sweat glands in newborn infants. In a few cases the erector pili muscles show heavy deposits. Dr. H. C. Trimble is very kindly making determinations of glycogen and sugar in normal and diabetic skins.

TABLE VIII.—GLYCOGEN CONTENT OF SKIN.

Type of treatment.	None.	Slight.	Moderate.	Marked.
No insulin	..	3	..	1
Insulin	..	1		..
Insulin, infection present	3	7	6	4
Control (nondiabetics)	..	3	15	18

Brain. In this series so few permissions for postmortem examination of heads have been received that there are insufficient data available. Geipel[15] found glycogen in the cortical cells of 14 out of 19 cases dying of diabetic coma.

Leukocytes. Glycogenic granules were found in the leukocytes of the granulocytic series in 18 cases of diabetes, all of which showed extensive deposits elsewhere typical of diabetes.

TABLE IX.—GLYCOGEN CONTENT OF LEUKOCYTES.

Type of treatment.	None.	Slight.	Moderate.	Marked.
No insulin	..	1	3	6
Insulin	..	1	..	..
Insulin, infection present	..	4	3	..
Control (nondiabetics) .	2	8	..	..

Discussion. Practically every case of active diabetes treated in the preinsulin days showed glycogenic infiltration of the epithelium of Henle's loops at autopsy. The presence of this lesion in cases of glycosuria makes one wonder whether or not it represents an attempt of the tubular epithelium to salvage some of the glucose being lost in the urine. Its absence in many cases treated with insulin shows that it is not an essential lesion of diabetes. This is also indicated by its presence in phloridzin diabetes.

There is close correspondence between increase in liver-cell glycogen and decrease in renal glycogen, and a similar relationship between liver-cell glycogen and liver-nucleus glycogen. As normal storage increases under the influence of insulin, pathologic storage decreases. This holds true in other organs as well. A diabetic responding satisfactorily to insulin treatment, and dying of some condition other than diabetes or sepsis, such as cerebral hemorrhage, shows very nearly the same distribution of glycogen as does the normal individual.

The advent of insulin treatment is dispoiling the pathologist of the one opportunity for the positive postmortem diagnosis of active diabetes.[16] The value of this means of histologic diagnosis is well shown by a recent case (No. 3928), where the diagnosis was established by the abnormal glycogen distribution. Miss A. P., aged sixty-nine years. Patient was supposed to have had mild diabetes, but diagnosis was never definitely established. In November, 1928, she developed left hemiplegia, and gradually grew worse, with mental deterioration. She showed no sugar in her urine, but this was presumably due to the low-caloric intake, which was little over that which would be allowed a moderately severe diabetic. Death occurred February 9, 1929, and an autopsy was performed three hours postmortem.

The chief cause of death was necrosis of cerebrum, secondary to arteriosclerosis. There was chronic pancreatitis, with sclerosis and hyalinization of the islands of Langerhans.

Best's carmine stain showed a slight amount of glycogen in the heart and voluntary muscle, a trace in the liver cells, much in the liver-cell nuclei, and a moderate amount in the epithelium of Henle's loops. On these findings, a diagnosis of diabetes mellitus was made.

The significance of the variation in glycogen content of the skin is as yet uncertain, but gives a reminder that this organ is by no means inconsiderable as a storehouse for glycogen. It is perhaps premature to attempt to correlate variations in cutaneous glycogen with the well-known susceptibility of the diabetic patient to cutaneous infections.

Conclusions. 1. Pathologic deposits of glycogen tend to disappear in insulin-treated cases of diabetes.

2. The normal storage of glycogen is increased in diabetic individuals by insulin treatment.

3. Sepsis decreases the effect of insulin so far as maintaining normal glycogen distribution is concerned.

4. The glycogen distribution may be a valuable aid in the postmortem diagnosis of active diabetes.

5. Glycogen in the renal epithelium may represent an attempt at salvage of the carbohydrate being lost in the urine.

6. Variations in glycogen deposits in the skin of diabetics may be related to their susceptibility to cutaneous infection.

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EARLY CHANGES PRODUCED IN DOGS BY THE INJECTIONS OF A STERILE ACTIVE EXTRACT FROM THE ANTERIOR LOBE OF THE HYPOPHYSIS.

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In a previous article[1] we have given the first account of Experimental Canine Acromegaly. In it we have shown the effects, on an English bull dog, of daily intraperitoneal injections of a sterile alkaline extract prepared from the anterior lobe of the hypophysis. It is the object of this paper to report on the early changes produced in dogs by such injections.

Experiment I. Two female foxhounds apparently thoroughbred littermates, were received on February 2, 1928. They were about four months old at that time, and resembled each other closely, as may be seen by the photograph taken March 19 (Fig. 1). On February 16, they weighed 3.9 and 3.6 kg. respectively. The heavier animal was reserved as a control, and the smaller one was given daily intraperitoneal injections of 15 to 20 cc. of sterile filtered anterior lobe extract.

The progress of their respective weights is shown by the chart (Fig. 2). The injected animal exceeded its control in weight within two weeks, and after three months of injections was approximately 50 per cent heavier.

The structural changes never became so marked as in the case of the injected English bull dog previously reported. The increase in height and weight was unmistakable, but not striking. The nose became long and thick, the skin loose and the abdomen protuberant. The paws became enlarged, and within two months of the beginning of injections, the animal became plantigrade instead of digitigrade (Figs. 3 and 4). The nipples became enlarged, but not the udders. There was no noticeable change in the vagina. Neither animal went into heat.

On May 23, it was noticed that the injected animal was losing weight and seemed sick. It died the next day, following administration of a purgative vermifuge.

Autopsy. *Gross Findings.* The cadaver was cold. Rigor mortis. Vomitus about the mouth. About 1 cm. of fat over the abdomen. Musculature well developed, and deep red in color.

The *thyroid* appeared somewhat enlarged. It was deep red in color, the acini plainly visible to the naked eye. There was a very large persistent *thymus* filling the entire superior mediastinum, and extending over the

pericardium to the diaphragm. The *heart* appeared normal. The *lungs* were injected, "downy" in consistency and free from pneumonic patches.

The *peritoneum* was full of a sanguineous fluid, perhaps 400 cc. in all. No source for it was found. The omentum contained much dark-green pigment, and the lymph glands were greatly enlarged. The *liver* was large, but appeared normal externally and on cut section. The *spleen* was large,

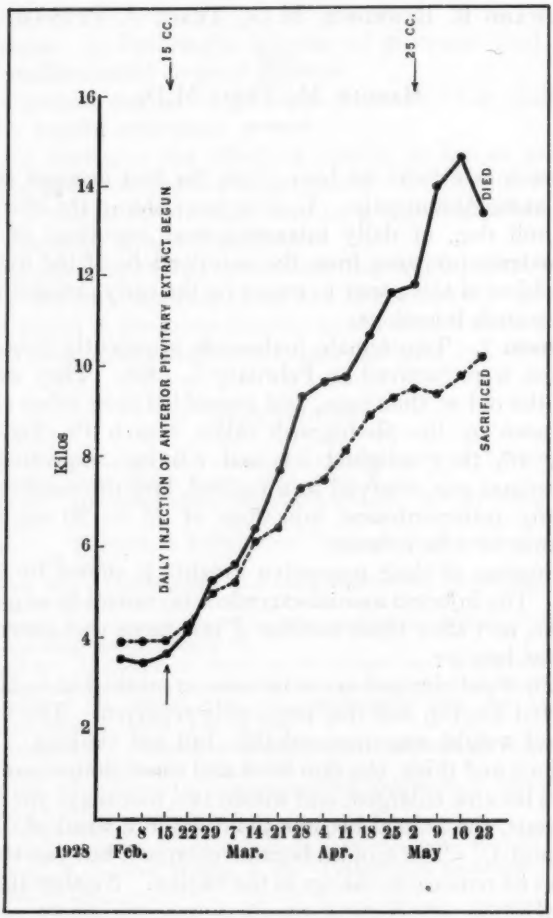

FIG. 2.—Chart of growth of the two animals. Weight in kilograms plotted at weekly intervals. The broken line indicates the control; the continuous line, the experimental animal.

soft and dark-blue in color. The *pancreas* appeared normal. The *kidneys* seemed perhaps a little enlarged. The *adrenals* were small. The *ovaries* and *uterus* were somewhat large for the age. There were neither large follicles nor corpora lutea in gross.

The *brain* was removed intact. It showed no gross abnormalities. The *hypophysis* appeared normal.

The control animal was sacrificed by etherization four days later. A complete autopsy was performed, but revealed no abnormalities. A comparison between the respective gross weights of the various organs in the two animals is given in Table I.

TABLE I.—FOXHOUNDS. COMPARATIVE WEIGHT OF ORGANS.

	Control hound, weight, gm.	Injected hound, weight, gm.	Increase in per cent.
Thyroid	1.50	3.000	100
Thymus	26.00	84.000	223
Heart	68.00	115.000	69
Liver	450.00	800.000	78
Spleen	21.00	42.000	100
Pancreas	28.00	45.000	60
Kidneys	56.00	136.000	143
Adrenals	0.75	1.000	25
Uterus	1.00	4.000	300
Ovaries	1.00	4.000	300
Brain	73.00	75.000	3
Hypophysis	0.07	0.075	7

Microscopic Findings. The *thyroid* of the injected animal already shows striking changes (Fig. 5). The cuboidal epithelium lining the glands is hypertrophied, thrown into folds, and is invading the lumen. There is an increase in the connective-tissue stroma as compared with that of the control animal. Whereas colloid is present in large amounts in the control, there is no colloid to be seen in the injected animal.

The *thymus* also shows a different structure in the two animals. The normal lobular arrangement seen in the control is very much less definite in the injected animal. There are fewer thymic corpuscles and fewer lymphocytes per high-power field in the injected animal. On the other hand, there is more fat and more edematous-tissue space.

Heart. No microscopic differences are noted between the two animals.

Lungs. Some of the alveoli in the injected animal are partly filled with a serous exudate. Those of the control are clear.

The *liver* shows certain quite definite changes, probably all attributable to the terminal infection (Fig. 6). There is a central necrosis which is hemorrhagic in character; in many areas there are fused hyaline masses of bloodclot. Throughout the sinuses there are more leukocytes present than in the control.

Neither the *spleen* nor the *pancreas* presents any microscopic differences in the two animals.

The *kidneys* show one very definite microscopic difference; namely, the glomeruli of the injected animal are unquestionably larger than are those of the control as established by comparing a large number of glomeruli under the oil-immersion lens. In the injected animal one glomerulus frequently extends beyond the limits of an oil-immersion field, whereas in the control no glomerulus can be found which quite fills the same field.

Adrenals. No microscopic differences are noted.

Uterus. Grossly this organ is four times the size of its control and microscopically the increase in size and development of muscular and endometrial tissue is very striking (Fig. 7).

Ovaries. The cells lining the follicles are elongated and columnar. In many places they have desquamated and filled the lumen. There is one irregular shaped cystic follicle containing an amorphous precipitate. There is some increase in the number of unripe follicles (Fig. 8).

Hypophysis. The anterior lobe appears to be edematous, with large intercellular spaces, but this may represent postmortem change. Otherwise the sections are similar in structure.

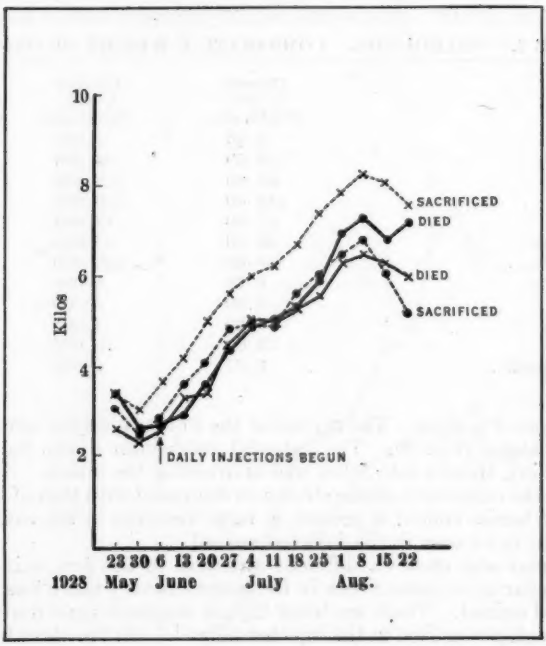

FIG. 10.—Chart of growth of the terriers. Weight in kilograms plotted at weekly intervals. The broken lines indicate the controls; the continuous line, the experimental animals. Disease and early death interfered with a satisfactory growth experiment.

Experiment II. Four female terriers, littermates resembling each other closely, were received in the laboratory on May 23, 1928, at which time they were ten weeks old (Fig. 9). They lived only three months longer, developing distemper in August, from which they died early in September. During their stay in the laboratory their progress was impaired by snuffles and minor upsets. After two weeks in the laboratory, daily injections of anterior-lobe extract were begun on the two smallest of the litter. Both became plantigrade about a month before their death. Their gain in weight is shown in the chart (Fig. 10). Disease and early death interfered with any appreciable increased rate of growth in the injected animals. Certain changes, however, had already taken place.

Autopsy. *Gross Findings.* One of the animals was not autopsied, as the body was in very poor condition, but a comparison of the weights of the organs of the other three is given in Table II. The striking feature is the enlargement of the heart and genital tract (Fig. 11) in the injected animal.

FIG. 1.—Littermate foxhounds on March 19, 1928, showing close resemblance early in experiment.

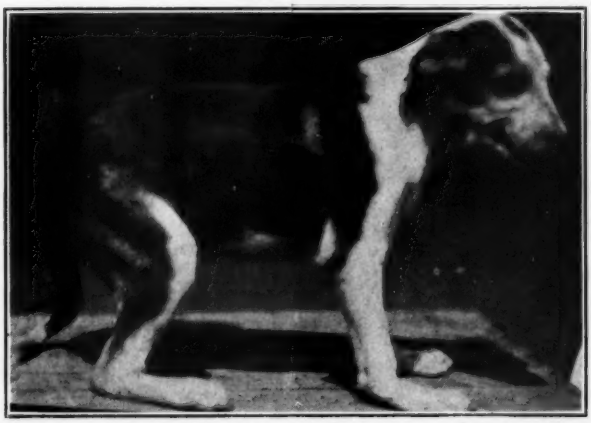

FIG. 3.—Experimental foxhound May 22, 1928, two months after injections were begun. Note plantigrade stance and inalert attitude, contrasted with control (Fig. 4).

FIG. 4.—Control foxhound, May 22, 1928. Compare with Fig. 3

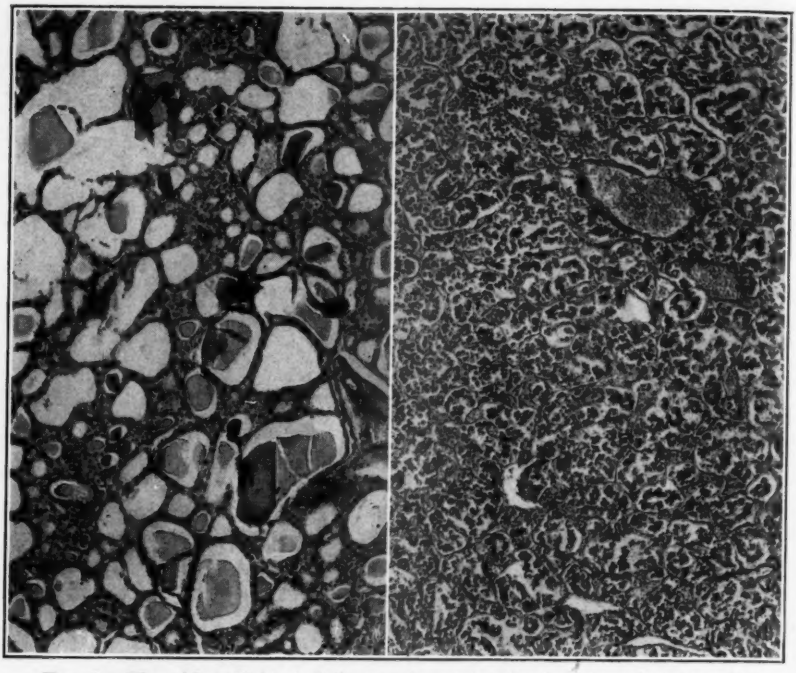

FIG. 5.—Thyroids: Control, left; experimental animal, right. Note hypertrophied epithelium, collapsed alveoli, and absence of colloid in the experimental animal; × 80.

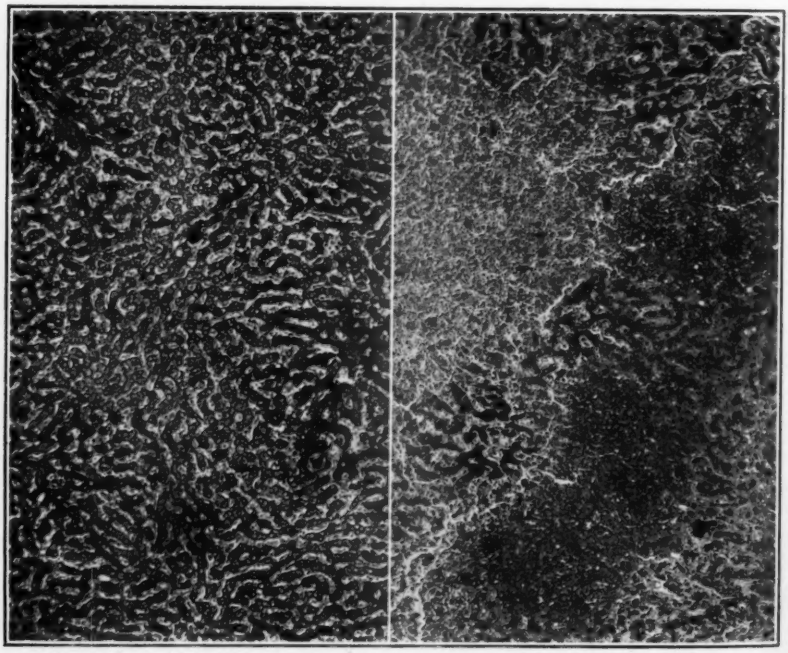

FIG. 6.—Liver: Control, left; experimental animal, right. Note necrotic areas, and leukocytic infiltration. × 80.

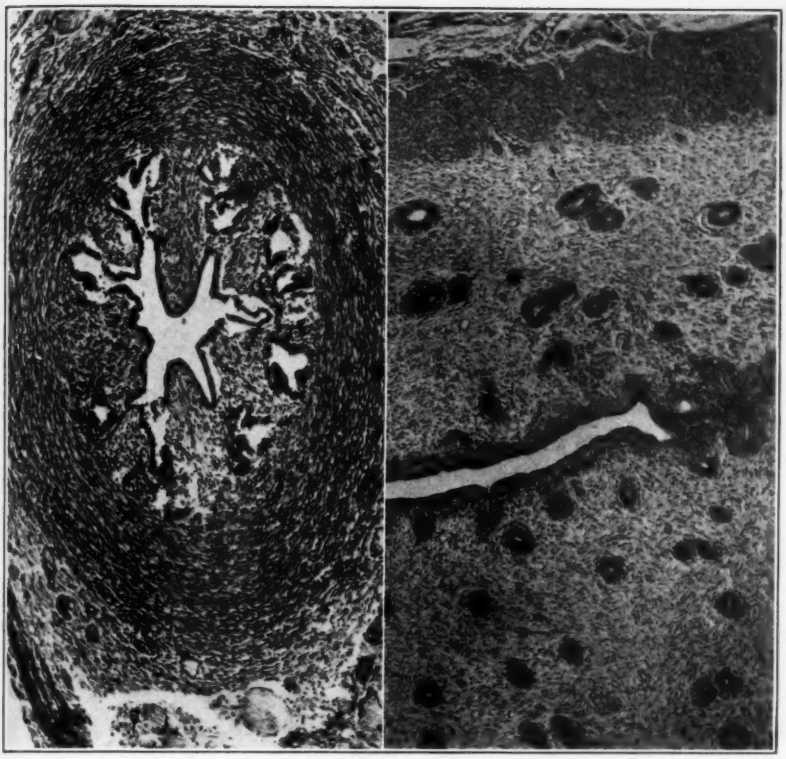

FIG. 7.—Uterus: Control, left; experimental animal, right. Note extreme difference in size and development. × 80.

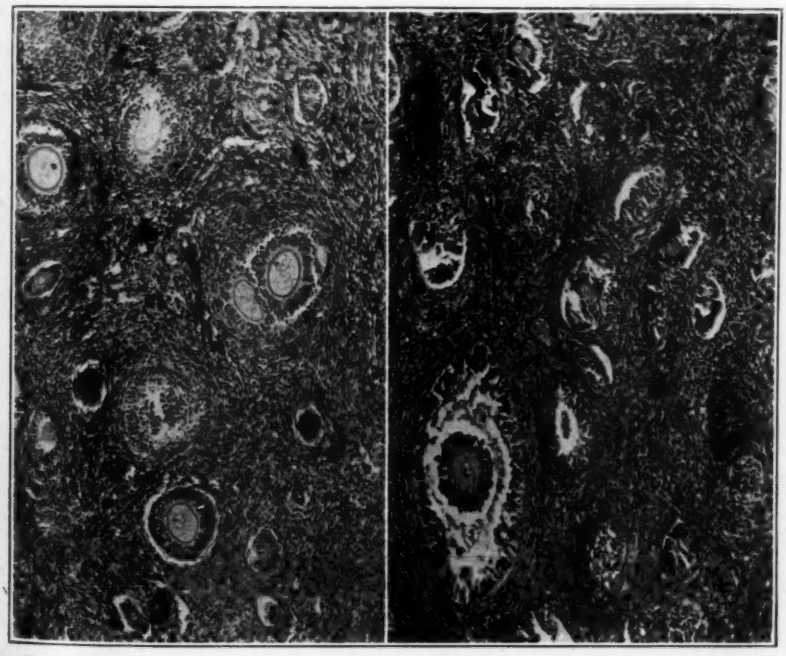

FIG. 8.—Ovary: Control, left; experimental animal, right. Note that there are no normal follicles in the experimental animal. × 80.

FIG. 9.—Littermate terriers when first received, May 30, 1928.

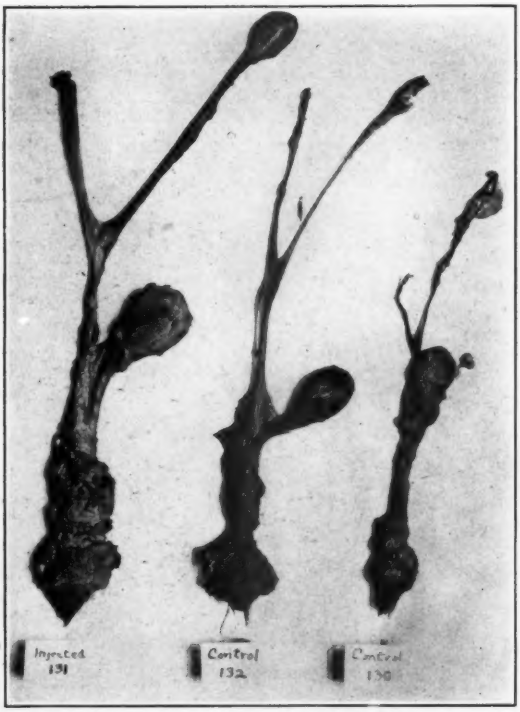

FIG. 11.—Terriers. Photograph showing comparative size and development of genital tracts.

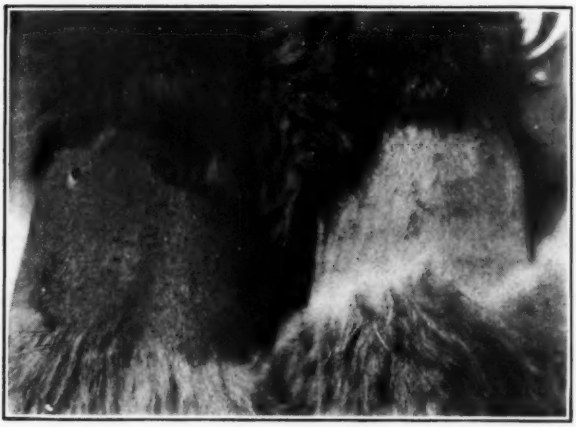

FIG. 13.—Collies, one week after shaving band of hair. Control animal on left shows hair already growing. Hypophysectomized animal on right shows almost no growth of hair.

FIG. 14.—Collies, two months after shaving band of hair. Control animal on right shows hair entirely grown. Hypophysectomized animal on left shows slight growth of hair with band still plainly visible.

FIG. 15.—Smallest hypophysectomized collie, showing liveliness two months after operation.

FIG. 16.—Smaller hypophysectomized collie with control, two months after operation.

FIG. 17.—Collies. Injected animal in front. Control, behind. Note early plantigrade position and general lack of interest of injected animal.

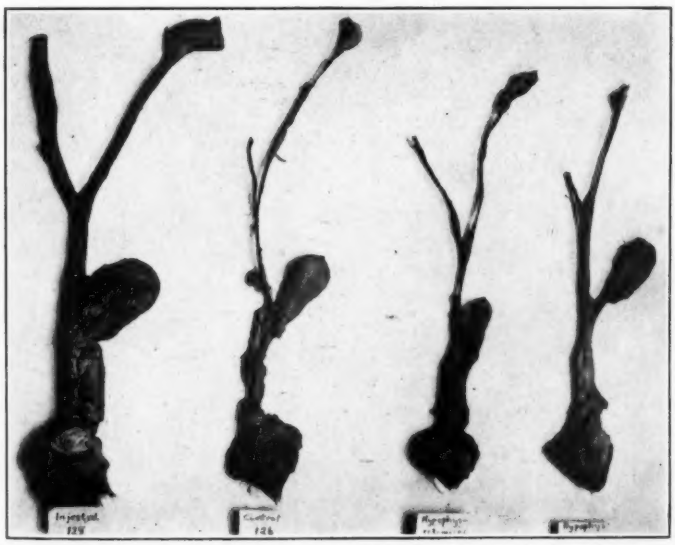

FIG. 18.—Photograph to show comparative size of genital tract in the four collies. Note how much larger is that of the injected animal on the left.

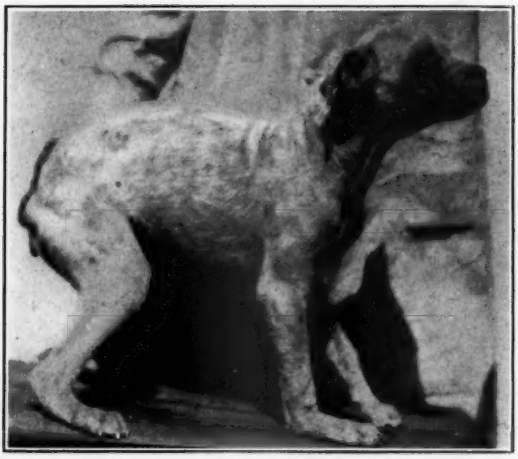

FIG. 19.—Male terrier after two months of injection, showing general weakness and plantigrade stance.

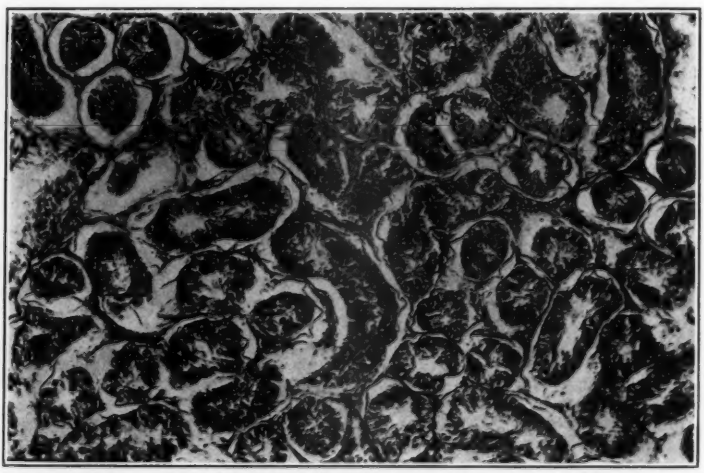

FIG. 20.—Testicle: showing degenerate structure with tissue invading the central portion of the tubules. × 80.

Whereas the other organs are smaller in the injected animal than in the larger control, the heart and genital tract are noticeably larger—the heart more than a third again as large, and the genital tract more than two and a half times as large.

TABLE II.—TERRIERS. COMPARATIVE WEIGHT OF ORGANS.

	Control.	Injected.	Control.
Thyroid	5.00	2	1.50
Heart	75.00	105	44.00
Liver	600.00	463	340.00
Spleen	28.00	23	23.00
Pancreas	32.00	?	12.00
Kidneys	84.00	66	62.00
Adrenals	4	3	2.00
Genital tract	24.00	63	19.00
Brain	72.00	70	68.00
Length of intestine in meters	4.82	4	4.18

Microscopic Findings. Certain changes are to be noted even at this eary date. The *thyroid* of the injected animal shows an absence of colloid whereas there is abundant colloid present in the control. The acini are in many places filled with débris which proves to be degenerated cells. The secreting cells are thrown into folds in some places as occurs typically in exophthalmic goiter, appearing also to be individually larger and more columnar in character than corresponding cells in the control section, which are relatively flat or cuboidal.

The *kidney* also shows the changes in the glomeruli noted in the previous experiment—namely, the actual size of the glomerulus of the injected animal is larger than the glomerulus of the control, as measured by comparison of each in the oil-immersion field.

Uterus. The walls are very much thickened and there is a considerable increase in endometrial tissue over that seen in the control. The appearance is similar to that shown in Fig. 7 (previous experiment).

Ovaries. In the injected specimen there is a very considerable increase in the number of follicles.

The sections from other organs do not present any definite change from the normal histology.

Experiment III. Four collies, littermate sisters, apparently pure-bred animals, were received in the laboratory on May 2, 1928, at which time they were two months old. They lived four months more, dying or being sacrified because of respiratory infection.

Two of the animals were completely hypophysectomized at the end of two weeks in the laboratory. Hypophysectomy was performed by the usual temporal route and the gland removed by suction. One animal was reserved as a control and the remaining one used for injections of anterior-lobe extract. The progress of these four animals in regard to gain in weight is shown in the accompanying chart (Fig. 12). It is evident that the two hypophysectomized animals stopped gaining weight about one month postoperative. Both the other animals continued to gain in an apparently normal manner, the injected animal gaining on the whole somewhat faster than the control, so that the former, although somewhat

lighter than the latter originally, was slightly heavier at the time of death.

Observations were made in these animals regarding the growth of hair. After they had been in the laboratory about three weeks a wide band of hair, completely circling the trunk in its midportion, was shaved, and the progress of the new growth of hair was carefully noted (Fig. 13). Two months after shaving, both the hypophysectomized animals showed the band very plainly (Fig. 14), and in

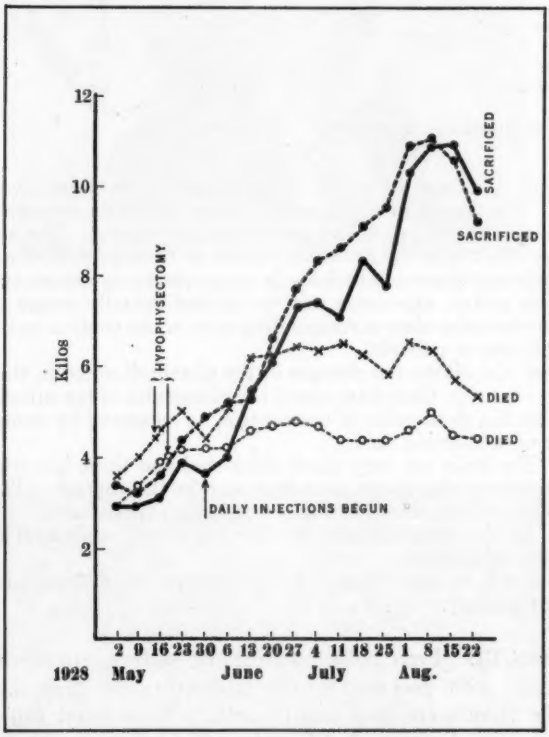

FIG. 12.—Chart of growth of the collies. Weight in kilograms plotted at weekly intervals. The continuous line indicates the injected animal; the broken line, the control; the two dotted lines, the hypophysectomized animals.

one of them there had been practically no growth of hair at all. In the control and the injected animals on the other hand, the hair had again become of normal length, there being no band visible. These findings coincide with our previous observations in this laboratory.[2] It is also interesting to note the liveliness of the operated and control animals as compared with the injected animal (Fig. 15). A comparison of the size and general appearance of three of the animals is given in the photographs (Figs. 16 and 17).

At the end of four months the two operated animals developed upper respiratory infection from which they died. The other two were also in poor condition and both losing weight. They were, therefore, sacrificed at the same time.

Autopsy. *Gross Findings.* The control animal showed very little of note except for slight bronchopneumonia and marked tracheitis.

The injected animal showed some abnormalities. There was slight prognathism and evident enlargement of the heart and genital tract (Fig. 18).

The Smaller Hypophysectiomized Animal. Subsequent microscopic examination showed that not quite all the anterior lobe was removed at operation; however, very little anterior-lobe tissue remained, and clinically there was almost complete cessation of growth. It was noted that the jaw was receding in character. The thyroid seemed particularly pale. The lungs showed definite bronchopneumonia. All the other organs appeared small, especially the uterus, tubes and ovaries.

The Larger Hypophysectomized Animal. In this case microscopic examination showed the operation to have been complete—no hypophyseal tissue remained. Here again the thyroid appeared pale. Otherwise the gross examination was not remarkable.

A comparison of the weights of the organs is given in Table III.

TABLE III.—COLLIES. COMPARATIVE WEIGHT OF ORGANS.

	Small ectomized.	Large ectomized.	Control	Injected.
Thyroid	1.00	?	1.00	2.00
Heart	40.00	47.00	98.00	112.00
Liver	250.00	80.00	750.00	700.00
Spleen	8.00	?	28.00	26.00
Pancreas	12.00	18.00	36.00	55.00
Kidneys	35.00	55.00	92.00	112.00
Adrenals	0.50	?	3.00	1.50
Genital tract	13.00	20.00	28.00	37.00
Brain	60.00	?	?	66.00
Length of intestine, meters	3.54	3.07	4.61	4.67

Microscopic Findings. Thyroid. The control animal shows normal structure and normal blue staining colloid present in the usual amounts (all sections stained with hematoxylin and eosin).

The injected animal shows the presence in some of the acini of moderate amounts of pink-staining colloid but many acini are filled with a cellular and amorphous débris. The epithelium lining the glands is hypertrophied, tending to be columnar in type and to invade the lumen in many places. There is an excessive amount of interglandular connective-tissue stroma.

The thyroid glands of the two hypophysectomized animals do not show any abnormality.

Heart. There are no unusual findings in any of the sections.

Liver. The only pathology noted in this organ was in the smaller hypophysectomized animal in which there were areas of central necrosis with fat infiltration into the trabeculæ.

Spleen and Pancreas. Sections from these organs all show essentially normal histology.

Kidneys. The glomeruli of the injected animal are already definitely larger than are those of the control or of the operated animals. There is no appreciable difference in size, however, between the glomeruli of the control as compared with the operated animals. In other respects the histology is not remarkable.

Adrenals. The adrenal glands show no definite abnormalities.

Uterus. There appears to be an unusually large amount of endometrial and connective tissue in the injected specimen and relatively little in the larger hypophysectomized specimen. The uterus of the smaller operated animal is very small and immature.

Ovaries. The ovary of the injected animal shows an increase in the number of unripe follicles but no ripening eggs. The ovary of the smaller hypophysectomized dog is particularly small and contains few follicles, none of which are mature.

Hypophysis. There are no microscopic changes seen. Serial sections through the hypophyseal region in the smaller operated animal show minute amounts of anterior hypophyseal tissue remaining. Similar serial sections in the larger operated animal show that hypophysectomy was complete. There is no evidence of injury to the floor of the third ventricle.

Experiment IV. A further experiment concerns the effect of injecting the anterior lobe extract in a male dog.

On February 2, 1928, we received in the laboratory a litter of 6 terriers, 3 males and 3 females. Unfortunately, 5 of them developed distemper and died before any noteworthy changes developed. One male, however, lived seven months in the laboratory, being received at the age of about two months and dying at the age of about nine months. Daily injections of 15 to 30 cc. of sterile anterior-lobe extract were carried out during the last three and a half months. After two months of injection the animal became markedly plantigrade (Fig. 19).

Autopsy. *Gross Findings. Jaw.* Well-marked prognathism was noted.

Thyroid. This organ was somewhat enlarged, red and hyaline in character.

The *thymus* was not identified.

The *lungs* showed bronchopneumonia.

The *liver* appeared unduly large (800 gm.) with particularly prominent architecture.

The *adrenal* cortex was slightly thickened and the medulla unusually pink.

The *testicles* were small.

Otherwise the organs were negative.

Microscopic Findings. The only organs presenting abnormalities were the thyroid and genitalia.

The *thyroid.* Some of the acini here are filled with cellular débris. There is an abnormally small amount of colloid in the cells and in the acini. The cells lining the acini are cuboidal.

Testicle. No sexual cells can be found which have developed beyond the spermatocyte stage. The central portion of the tubules is occupied by strands of degenerate tissue (Fig. 20).

Epididymis. The cells lining the ducts are cuboidal and possess no cilia.

Penis. This organ resembles that of an immature animal and contains little erectile tissue.

Summary and Conclusion. The experiments reported here confirm our earlier observations on experimental hyperpituitarism and show particularly the early changes resulting from daily injection of a sterile active anterior-lobe extract.

After only three months of injection there are noted very definite changes in the thyroid gland and in the genital tract.

The changes in the thyroid consist in hypertrophy of the gland epithelium with invasion of the lumen and almost complete absence of colloid.

As to the genital tract, both male and female were sexually inactive. In the female there is an hypertrophy of the uterus, ovaries and vagina. In the male there is no hypertrophy, the testicles being small and showing only the earliest stages of spermatogenesis.

Skeletal overgrowth and splanchnomegaly were noticeable in the case of the foxhounds after three months of injection.

Sluggishness, inalertness and plantigrade stance were all noted after two months of injection.

A comparison was made between hypophysectomized and normal animals. Cessation of growth after hypophysectomy was confirmed. A marked slowing in the rate of growth of hair was noted. Normal alertness was not interfered with by hypophysectomy.

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THE DIFFUSIBILITY OF CALCIUM IN BRONCHIAL ASTHMA AND ALLIED DISORDERS, AND IN PULMONARY TUBERCULOSIS.

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Bronchial asthma has been studied from many angles. At the present time there is no single factor which can be regarded as responsible for the paroxysms. As stated by Pottenger,[1] "the underlying reacting capacity of the individual's bronchial neuromuscular mechanism must be taken into consideration as well as the exciting cause. . . . When all the facts are carefully weighed the argument seems strongly supported that there is something in the make-up of the asthmatic patient which makes him susceptible to the action of proteins, climatic change, and physical and chemical irritants." The nature of the tissue state which constitutes the basis for this susceptibility is not known. Many theories have been advanced, among which is that of calcium deficiency.

The elaboration of this theory is dependent upon certain physiologic and pharmacologic facts and upon clinical observation, but it has not been supported by any substantial experimental evidence. From a physiologic viewpoint, the asthmatic paroxysm may be considered a condition of local vagotonia, as suggested by Eppinger and Hess.[2] In the light of our present knowledge of the vegetative nervous system and its functional interrelationships, vagotonia must be interpreted in a broader sense than as merely a disturbance of autonomic nervous balance. Ringer[3] many years ago demonstrated the pharmacologic antagonism of calcium and sodium and potassium, and showed that a proper balance between these elements is necessary for the preservation of normal cardiac function. More recent studies by Howell and Duke,[4] Kolm and Pick,[5] Kraus and Zondek,[6] Andrus and Carter,[7] Loewi,[8] Petersen[9] and many others have established the relationship between autonomic balance and the ratio of calcium to sodium and potassium in the tissues. These studies indicate that vagotonia (parasympathicotonia) is associated with a diminished calcium-potassium and calcium-sodium ratio. This suggested relative or actual calcium deficiency has been assumed by some as a logical basis for calcium therapy in bronchial asthma and allied disorders.

This assumption has met with vigorous opposition because of the fact that a calcium deficiency has not been satisfactorily demonstrated in these conditions. Practically all of the experimental studies in this connection, at least in human beings, have concerned themselves with the determination of the calcium content of blood serum. A recent study by Criep and McElroy[10] of 167 cases of atopy, including asthma, hay fever, vasomotor rhinitis, urticaria and angioneurotic edema showed the level of serum calcium to be within normal limits in the great majority of instances, a few being slightly below and above normal. Greenbaum,[11] in a study of 63 patients with urticaria, found normal or elevated serum calcium values in all but one. Schamberg and Brown[12] and Schwartz and Levin[13] reported similar negative findings. Novak and Hollander[14] found a suggestive diminution in serum calcium in vasomotor rhinitis but not in hay fever and asthma, while Sonnenschein and Pearlman[15] reported normal findings in vasomotor rhinitis. There is some contradictory evidence which, however, does not seem very convincing. For example, Brown and Hunter,[16] regarding any figure below 9.6 mg. as subnormal, believe that a calcium deficiency exists in a large proportion of all patients with atopic disorders. It must apparently be concluded that the bulk of evidence points to the fact that in the great majority of such cases the blood-serum calcium is within normal limits.

In spite of these findings, calcium salts are extensively employed in the treatment of bronchial asthma, urticaria and allied conditions. There can be no doubt that such therapy is of distinct benefit in

many cases. Because of the normal serum calcium values, it is believed by most workers in this field that the clinical improvement is due to the depressing action of calcium and to its inhibiting influence upon cell permeability. A few, however, still maintain that there may be a disturbance of calcium balance not readily demonstrable by ordinary means. Hanzlik,[17] in a review of the problem of allergy, states that calcium salts prevent or inhibit experimental edema and clinical allergic manifestations, owing presumably to their power to lessen cellular permeability, indicating indirectly therefore the possible physical basis for the reactions produced by many agents.

Until modern chemical methods made possible more exact studies of mineral balance, many believed that pulmonary tuberculosis was associated with a process of demineralization. At the present time, however, there is no evidence to support this theory; no significant decrease in the calcium content of blood or tissues has been demonstrated and no increase in calcification of tuberculous lesions has been found after calcium administration. The subject has been reviewed by Wells[18] and by Gordon and the writer.[19] Since the early studies of von Pirquet,[20] the relation of the allergic state to reinfection in tuberculosis has been thoroughly investigated. There seems to be no doubt that the "second infection" or "adult type" of pulmonary tuberculosis is characterized by a preëxisting and coexisting state of hypersensitiveness to the tubercle bacillus and its products. Therefore, from this standpoint, the pathologic physiology of the tissues in "adult" pulmonary tuberculosis and in bronchial asthma should have certain features in common. If a disturbance of calcium balance is an essential feature of allergic disorders it should likewise exist in this form of tuberculosis. As stated previously no calcium deficiency has been demonstrated. Halverson, Mohler and Bergeim[21] and Sweany, Weathers and McClusky[22] have found the serum calcium in most patients with tuberculosis to be within normal limits, and furthermore, there seems to be no constant relationship between the blood-calcium level and the extent or activity of the pulmonary lesion.

It may be quite definitely asserted that in the great majority of patients with some manifestation of allergy or hypersensitiveness the serum calcium is within normal limits. This fact, however, does not of itself justify the conclusion that there is no disturbance of calcium balance in these conditions. The subject of calcium metabolism is quite involved and there is still much to be learned concerning it, but certain facts have been rather definitely established. An understanding of the condition of calcium in the blood and tissues is essential to the proper appreciation of the manner in which the calcium balance may be disturbed in disease.

The normal serum calcium concentration is from 9 to 11 mg. per 100 cc. Physiologically this exists in two states, termed diffusible

and nondiffusible. The diffusible fraction is that portion which is capable of passing through the capillary walls and cell membranes; the nondiffusible normally cannot, being bound in some way, it is believed, to the serum proteins. In a previous study[23] the normal figures for diffusible calcium were found to be 4.5 to 5.5 mg. per 100 cc., those for nondiffusible calcium being 4.7 to 5.75 mg. per 100 cc. In addition, a portion, estimated at about 20 per cent of the total, probably exists in ionized form, the remainder being unionized. These facts are obviously of great importance for the pharmacologic properties of the various calcium states must be quite different. The production of a calcium effect is dependent not so much upon the level of calcium in the blood as upon its distribution in the blood and tissues. This may perhaps be best expressed by the ratio of the diffusible to the nondiffusible, and of the ionized to the unionized fractions, the latter of which cannot be satisfactorily determined by present methods. These points may be illustrated by the following equation:

Total serum calcium	=	Diffusible calcium	+	Nondiffusible calcium
9 to 11 mg.		4.5 to 5.5 mg.		4.7 to 5.75 mg.
		(1) Ionized 2 mg.		Unionized
		(2) Unionized		

It can readily be seen that alterations in these ratios may occur without any change in the amount of serum calcium.

The maintenance of the normal calcium balance is dependent upon many factors, among which are the nature and amount of serum proteins, the parathyroid hormone, the concentration of phosphate and carbonate ions and the hydrogen-ion concentration. The manner in which these factors operate cannot be gone into, but there is no question of the occurrence of disturbances of calcium balance as indicated by alterations in the proportions of the diffusible and the ionized fractions, the total serum calcium being within normal limits. For example, in certain forms of tetany dependent upon a condition of alkalosis, the serum calcium level is often normal, the symptoms being due to a diminution in the proportion of ionized calcium. Then too, in jaundice there is some disturbance of the availability or utilization of calcium, although the serum calcium level may be normal or above normal. This is illustrated by the studies of Bowler and Walters[24] and of Dodek, Gordon and the writer.[25] The point of special significance in connection with the present study is the fact that the amount of serum calcium is not always a true index of the state of the calcium balance.

The vital importance of the preservation of the normal calcium distribution is probably due, in a large degree, to the influence of this element upon the permeability of the cell membrane. The functional activity of the cell depends upon the exchange of material between its interior and exterior, the permeability of the cell membrane being the determining factor in this exchange. It is well

recognized and readily demonstrable that normal permeability is dependent to a considerable extent upon the presence of a normal balance between the inorganic ions in the fluid bathing the cell. Calcium diminishes cell permeability; in fact, Loeb[26] attributes the general inhibiting action of calcium to this property. The possible significance of this fact in connection with the problem of hypersensitiveness is apparent in the light of the observations of many investigators summed up in the statement by Manwaring,[27] that increased capillary permeability will ultimately be found to be the dominant fundamental characteristic of protein sensitization and anaphylaxis. It is of interest to note that Petersen[9] found abnormal degrees of permeability of skin capillaries in patients with pulmonary tuberculosis. The possible relation of this observation to the hypersensitive state of the tissues in tuberculosis is a point worthy of consideration.

Present Investigation. The present investigation consists of the determination of the diffusibility of calcium in 25 patients with bronchial asthma, 3 with mucous colitis, 2 with vasomotor rhinitis, 1 with angioneurotic edema and 63 with pulmonary tuberculosis.

Method. There are two ways in which the diffusibility of calcium may be estimated: (1) by ultrafiltration or dialysis through an artificial membrane; (2) by the determination of the calcium content of cerebrospinal fluid. Under normal conditions the figures obtained by the two methods are practically identical. It must be realized, however, that the diffusibility of calcium in the body is dependent upon two variable factors; namely, the condition of calcium in the blood stream and the permeability of the capillary walls and cell membranes. When ultrafiltration or dialysis is employed the latter factor is disregarded, a fact which is of particular importance in connection with the conditions under consideration since it is believed that they are associated with or dependent upon an increase in cell permeability. This has been discussed more fully in a previous communication.[23] The method employed in this study consists in the determination of the calcium content of blood serum and cerebrospinal fluid withdrawn at the same time in each case. The calcium determinations were made by the Clark-Collip modification of the Kramer-Tisdall procedure.[28] The spinal fluid calcium is termed diffusible although "diffused" is probably more correct. The difference between this figure and the total serum calcium is the nondiffusible portion.

The pertinent data are presented in the accompanying tables.

Discussion. *Atopic Disorders.* The serum calcium in this series ranged from 7 to 12.67 mg. per 100 cc., 6 being below 9 mg. and 2 above 11 mg. per 100 cc. The detailed findings are presented in Table I. In a previous study[23] the normal cerebrospinal fluid calcium concentration was found to be from 4.50 to 5.50 mg. and the nondiffusible from 4.7 to 5.75 mg. per 100 cc., the ratio of

diffusible to nondiffusible calcium being 82 to 115 per cent. In the group of patients with atopic disorders the spinal fluid calcium ranged from 4.39 to 6.33 mg. per 100 cc., 20 being above and 1 below normal. The nondiffusible calcium varied between 1.5 and 7.5 mg., 2 being above and 22 below normal. The ratio of diffusible to nondiffusible calcium was from 68.9 to 400 per cent, 23 being above and 2 below normal.

TABLE I.—THE TOTAL SERUM CALCIUM, THE DIFFUSIBLE AND NONDIFFUSIBLE CALCIUM, AND THE RATIO OF DIFFUSIBLE TO NONDIFFUSIBLE CALCIUM IN 31 PATIENTS WITH ATOPIC DISORDERS AND 63 WITH PULMONARY TUBERCULOSIS.

Condition.	Cases.	Serum.*	Diffusible.*	Nondiffusible.*	Ratio, diffusible to nondiffusible.*
Asthma	25	7.00 to 12.67	4.39 to 6.33	1.50 to 7.50	68.9 to 400
Mucous colitis	3	9.84 to 11.0 0	5.62 to 6.00	4.22 to 5.00	120 to 133
Vasomotor rhinitis	2	10.55 to 10.70	5.75 to 6.10	4.45 to 5.00	115 to 137
Angioneurotic edema	1	8.2	5.5	2.7	203
Pulmonary tuberculosis	63	8.10 to 13.80	4.00 to 7.75	3.34 to 8.87	56.7 to 152

* Calcium values expressed in mg. per 100 cc. Ratios expressed as percentage.

There are factors other than the diffusibility of calcium which may influence its concentration in the cerebrospinal fluid. One of these is an inflammatory condition of the brain or meninges. This was present in no instance in this series. It is also theoretically possible that the level of calcium in the spinal fluid may be altered by changes in the intracranial venous and arterial pressures resulting in variations in the filtration of constituents of the blood plasma into the subarachnoid space. If this factor is operative the concentration of other poorly diffusible constituents of the spinal fluid, such as glucose, should be correspondingly altered. Glucose determinations were carried out in 18 of the 25 patients with bronchial asthma. The blood sugar varied from 86 to 102 mg., and the spinal fluid sugar from 46 to 56 mg. per 100 cc., showing no evidence of increased filtration pressure. The increase in the level of calcium in the cerebrospinal fluid is in all likelihood, therefore, dependent upon one or both of two conditions: (1) an actual increase in the diffusibility of serum calcium; (2) a selective increase in the permeability of the cell membranes and capillary walls. Since there is no indication in this group of cases of any locally operating factor in the brain, cord or meninges, these observations may be postulated as being representative of conditions existing throughout the tissues.

These findings seem to be indicative of a state of increased calcium diffusibility in atopic disorders. There has been very little investi-

gation of this problem. Blum, Delaville and Caulaert[29] found an increase in diffusible calcium in the rabbit and the dog during peptone shock. Brown and Ramsdell[30] studied the diffusibility of calcium in anaphylactic shock in guinea-pigs by the artificial membrane method. In the shocked animals there was a considerable increase in the diffusible fraction of serum calcium, the total calcium being essentially unaltered. Similar changes were observed following the administration of histamin. These observations coincide with our findings in bronchial asthma and allied disorders. The exact significance of this state of increased calcium diffusibility is a matter for conjecture. However, in view of the intimate relationship between cell permeability and inorganic-ion balance these observations appear to be of fundamental importance.

Pulmonary Tuberculosis. The serum calcium values in the group of 63 patients with pulmonary tuberculosis varied from 8.10 to 13.80 mg. per 100 cc., 17 being above 11 mg. and 2 below 9 mg. The cases have been divided into 3 groups accordingly as the ratio of diffusible to nondiffusible calcium was normal, increased or decreased. The abnormal findings are presented in Tables II and III.

TABLE II.—SIXTEEN CASES OF PULMONARY TUBERCULOSIS WITH RATIO OF DIFFUSIBLE TO NONDIFFUSIBLE CALCIUM ABOVE NORMAL.

Case.	Serum.*	Diffusible.*	Nondiffusible.*	Ratio, diffusible to nondiffusible.*	Lesion.
6 . . .	10.29	5.88	4.41	133	Exudative; advanced.
9 . . .	8.50	5.00	3.50	142	Exudative; advanced.
11 . . .	10.00	5.50	4.50	122	Proliferative; active.
17 . . .	8.10	4.76	3.34	142	Exudative; advanced.
18 . . .	10.00	5.71	4.29	133	Exudative; advanced.
21 . . .	10.00	5.71	4.29	133	Exudative; advanced.
23 . . .	9.52	5.28	4.24	125	Exudative; advanced.
25 . . .	10.56	5.85	4.71	124	Exudative; advanced.
28 . . .	10.56	6.13	4.43	138	Exudative; advanced.
37 . . .	9.38	5.67	3.71	152	Exudative; dying.
53 . . .	10.00	5.75	4.25	135	Exudative; advanced.
55 . . .	10.50	5.75	4.75	121	Exudative; advanced.
59 . . .	11.57	6.48	5.09	127	Exudative; advanced.
77 . . .	13.00	7.75	5.25	128	Exudative; advanced.
104 . . .	9.36	5.61	3.75	147	Exudative; dying.
114 . . .	8.63	4.65	3.98	117	Exudative; dying.

* Calcium values expressed in mg. per 100 cc. Ratio expressed as percentage.

In 16 patients the diffusibility ratio was from 117 to 152 per cent as contrasted with the normal range of 82 to 115 per cent. With one exception, (Case 11), the lesions, by Roentgen ray examination,

were of the exudative type, in an advanced stage. All were clinically active and 4 in a critical condition.

In 11 patients the diffusibility ratio was from 56.7 to 80.1 per cent. In each case the lesion was of the proliferative or fibroid types, 3 of the patients showing evidence of advanced peripheral arteriosclerosis. In 3 instances the process was quiescent and no one in this group was critically ill.

The 36 patients with diffusibility ratios within normal limits presented no constant clinical features. All were suffering with chronic ulcerative tuberculosis in varying stages of activity. In this group there appeared to be no correlation between the calcium distribution and the nature or extent of the pulmonary lesion.

TABLE III.—ELEVEN CASES OF PULMONARY TUBERCULOSIS WITH RATIO OF DIFFUSIBLE TO NONDIFFUSIBLE CALCIUM BELOW NORMAL.

Case.	Serum.*	Diffusible.*	Nondiffusible.*	Ratio, Diffusible to nondiffusible.*	Lesion.
12 . .	11.50	5.00	6.50	76.9	Proliferative.
27 . .	11.32	4.71	6.61	71.2	Proliferative; quiescent.
38 . .	13.80	4.93	8.87	56.7	Proliferative arteriosclerosis.
54 . .	11.50	5.00	6.50	76.9	Fibroid tuberculosis.
76 . .	10.50	4.00	6.50	61.5	Fibroid arteriosclerosis.
81 . .	12.68	4.87	7.81	62.3	Fibroid arteriosclerosis.
96 . .	9.55	4.25	5.30	80.1	Proliferative.
97 . .	9.60	4.20	5.40	77.7	Proliferative; quiescent.
102 . .	12.19	4.87	7.32	66.5	Fibroid; arteriosclerosis.
103 . .	12.19	4.87	7.32	66.5	Proliferative; quiescent.
105 . .	10.72	4.65	6.07	76.6	Fibroid tuberculosis.

* Calcium values expressed in mg. per 100 cc. Ratio expressed as percentage.

The exact significance of this variation in calcium diffusibility in tuberculosis is difficult to determine. If it is related in any way to the question of allergy it would appear logical to assume that the relationship should be a more constant one, since in all the patients included in this series the disease was of the "adult" or "second infection" type. It appears, however, that an increased ratio of diffusible to nondiffusible calcium is associated with the exudative type of tuberculous process with manifest clinical activity; conversely, a subnormal diffusibility ratio is associated with a predominantly productive or fibrotic lesion of low-grade activity. This finding is of interest in view of the observation by Petersen[9] that a fibrotic tuberculous lesion is accompanied by a diminished permeability of skin capillaries as determined by the blister test, and by an increased calcium-potassium ratio in the tissues; the reverse is the case in the exudative type of lesion.

In tuberculosis, as in bronchial asthma and allied disorders, there appears to be a definite relationship between calcium diffusibility and cell permeability. Which is the primary and which the secondary factor, or whether both are secondary to an allergic state cannot be determined by the method employed in the present study. However, from the findings of Brown and Ramsdell,[30] referred to above, it seems that the increase in diffusible calcium in anaphylactic shock is not dependent upon increased cell permeability, since the determinations were made by the artificial membrane method.

Conclusions. Previously reported investigations of calcium balance in allergic or atopic disorders and in pulmonary tuberculosis have concerned themselves with the determination of total serum calcium and of calcium intake and output. These studies have, in the great majority of instances, revealed no deviation from the normal and have led to the belief that no demonstrable disturbance of calcium metabolism exists in these conditions. Since the work of Rona and Takahashi,[31] establishing the partition of serum calcium into diffusible and nondiffusible fractions, considerable evidence has accumulated to indicate that the physiologic activity of calcium is dependent upon the various forms in which it exists. A disturbance of the ratio between the diffusible and nondiffusible fractions may occur, with distinct physiologic effects, without any alteration in the level of total serum calcium.

The present study appears to indicate that in bronchial asthma and allied disorders there is a definite and quite constant disturbance of calcium balance in the form of an increase in the ratio of diffusible to nondiffusible calcium. It is conceivable that this observation is related in some way to the increased capillary and cellular permeability which is believed to exist in these conditions.

In chronic pulmonary tuberculosis there is considerable variation in the diffusibility of calcium. It seems that an increased diffusibility ratio is associated with an exudative type of lesion with a high degree of clinical activity, while a decreased diffusibility ratio is associated with a productive process, relatively benign clinically. Whether or not these findings bear any relation to the problem of allergy in tuberculosis cannot be stated definitely but the implication is obvious.

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AURICULAR FIBRILLATION IN PATIENTS WITH GOITER.

I. Value of Quinidin Based on the Study of 114 Cases.

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Auricular fibrillation is the most frequent abnormal rhythm of the heart in goiter patients. Its treatment, therefore, is one of the problems in preoperative and postoperative management. Thyroidectomy alone will often bring about regular heart action,[1,2,3,4,5] although this may not take place for months or even years following complete subsidence of thyroid toxicity. (Cases 42, 43, 44, 45 and 46.) With the object of attempting to restore all such cases to normal rhythm before discharge from the hospital, this work was begun.

It is well known that auricular fibrillation is prone to recur in nonthyroid cases after successful treatment with quinidin. Levine and Wilmaers[6] found that only 4 of a group of 13 successfully treated with quinidin maintained normal rhythm more than a month afterward, and none after nine months. They conclude that quinidin should not be used in those patients who previously have had congestive heart failure. Sidel and Dorwart[7] are more optimistic in their report of failure cases. They used, however, much larger doses than is customary. Phillips and Anderson[10] report 59 cases of continuous auricular fibrillation in goiter patients, 52 per cent of which were found to have normal rhythm three to six months after thyroidectomy. Quinidin was used in some of these cases. Hamilton[3] estimated that 30 per cent returned to normal rhythm after thyroidectomy.

This report deals with 59 cases of postoperative paroxysmal auricular fibrillation and 55 cases of established auricular fibrillation treated in the Lahey Clinic. All of the latter were at one time or another associated with hyperthyroidism, while a few of the former followed operation for nontoxic goiters. Eighteen patients of the established group had had congestive heart failure on admission to the hospital. The diagnosis was made chiefly by auscultation in the paroxysmal type, while electrocardiographic tracings were done in practically all of the established group. Only those patients who showed auricular fibrillation on admission to the hospital and continued to have it until a day or so before operation (not less than seven days in any instance) were classed as having established fibrillation. While this report does not represent a truly consecutive study of all patients operated upon in the Clinic during this

period of observation, it approaches this ideal insofar as the author was able personally to examine and treat them.

Paroxysmal Auricular Fibrillation. In most instances this type is seen following operation. It occurs frequently following removal of nontoxic goiters, but more often after partial or subtotal thyroidectomy in patients with primary hyperthyroidism. It is frequently disturbing to the patient, but rarely does it produce any alarming systemic reaction. Its appearance, therefore, cannot be considered as a cardiac emergency. Treatment, in most instances, is indicated only for the comfort of the patient.

We had frequently used digitalis in 12- to 18-grain doses to slow this type of irregularity. Often auricular fibrillation ceased following its administration. When this study was begun, we felt it desirable to observe a controlled group to determine if digitalis were effective in stopping paroxysms. Some, therefore, were given quinidin, others digitalis, while many received neither drug. Of 59 cases of postoperative auricular fibrillation (Table I) associated with thyroid disease, 15 were given digitalis as soon as possible within twenty-four hours after the onset. In 10 of this group, auricular fibrillation ceased within twenty-four hours after the drug had been administered, while 2 continued to have this irregularity from twenty-four to forty-eight hours. One of these was stopped with quinidin and the other stopped without further medication. Three more persisted after seventy-two hours and were then successfully stopped with quinidin. Another group of 29 patients received no cardiac medication at the onset of their paroxysms. All but 7 of these stopped spontaneously within seventy-two hours. The remaining 7 were given quinidin with success. Another group of 13 received quinidin as soon as possible after the onset and stopped during the time of quinidin administration. In view of the fact that the total time during which quinidin was given was usually less than twelve hours and that all cases in this group who received quinidin ceased to have fibrillation within this time, it becomes fairly conclusive that quinidin was effective. Furthermore, a few of the digitalis group persisted after digitalizing doses of digitalis. Since these were then stopped during quinidin administration and in view of the large number that stopped spontaneously this analysis contains no evidence to show that digitalis has any action in stopping paroxysmal fibrillation. Consequently, we have discontinued the use of digitalis in this group and use quinidin only if the irregularity is distressing to the patient or if it persists after two or three days.

Established Auricular Fibrillation. Approximately 10 per cent of patients with hyperthyroidism show this abnormality. Over 90 per cent of those patients who have frank congestive heart failure associated with hyperthyroidism have this irregularity and, conversely, from 30 to 40 per cent of those having auricular fibrillation

have a history or show various degrees of this type of heart failure. Thus, from a therapeutic point of view, this group requires more consideration than the group just discussed. The possibility of embolism is to be considered in selecting these patients for quinidin therapy.

During this period of observation (June, 1927 to September, 1928), we have seen 4 cases of embolism in thyroid patients. It is well to point out that 2 of these (Cases 11 and 17) had mitral stenosis with large multiple adenomatous goiters with questionable toxicity. Quinidin was tried in the first instance without success following operation. One month later while taking digitalis the patient developed a hemiplegia at home, almost certainly from an embolus. In the second case, operation was performed without incident. One week later the patient was digitalized, the apex rate came down to sixty and multiple emboli were dislodged. Such accidents following digitalization are not infrequent in nonthyroid cases. We have never seen it in the auricular fibrillation associated with well-marked hyperthyroidism and we feel that the over-activity of the heart from thyroid toxicity tends to prevent the formation of the auricular thrombi.

The other 2 cases showing emboli were very similar (Cases 13 and 14). Both had long been known by their families and physicians to have goiters. Examination revealed symmetrical enlargement of the thyroid. Thyroid toxicity was of the mild type, but from their history it had been of a severe grade previously. Both came to us with embolic manifestations and were not operated upon. One died of thrombosis of the femoral artery and infarcts of the lung. At autopsy, there were thrombi in both auricles. The valves were normal. The other case, showing a residual hemiplegia on admission, was sent home and died suddenly one month later. On clinical examination, the heart showed no evidence of valvular disease, although there was considerable enlargement. There was also marked arteriosclerosis and a deficient renal function.

We feel these last 2 cases illustrate what may happen to a long-standing case of hyperthyroidism without operation and restoration to normal rhythm, and furthermore establish another group in which one should be cautious regarding quinidin until the relationship of quinidin to embolism is established.

Selection of Cases. We exclude from quinidin therapy any patient who has:

1. A history or clinical evidence of embolism.
2. Marked mitral stenosis with fibrillation of unknown duration.
3. Mitral stenosis with congestive heart failure.
4. Congestive heart failure associated with large feebly pulsating heart as determined by fluoroscopy.
5. Long-standing fibrillation in hyperthyroid patients in which the hyperthyroidism is of mild degree.

TABLE I.—SUMMARY OF RESULTS IN 57 CASES POSTOPERATIVE PAROXYSMAL AURICULAR FIBRILLATION.

	Untreated	Treated with digitalis.*	Treated with quinidin.†
Management during first twenty-four hours	29	15	13
Stopped during first twenty-four hours	19	10	13
Stopped during twenty-four to forty-eight hours	1	2‡	1
Stopped during forty-eight to seventy-two hours	2	1	
Persisting after seventy-two hours	7§	2§	9
Persisting after quinidin	0	0	0

* Dose digitalis varied from 10 to 29 grains.
† Average dose quinidin, 19.5 grains (3 to 39 grs.).
‡ One of these cases treated with quinidin.
§ All these treated with quinidin.

Of 55 cases of established auricular fibrillation, 7 stopped spontaneously (Table II), 8 were not given quinidin (Table III), and in 5 other cases quinidin was not successful (Table IV). Thirty-four cases were successfully treated, 4 of which recurred (Table V). Of the 34 cases successfully treated, 30 were first given treatment after operation (Table VI), while 4 of these had been given quinidin successfully before thyroidectomy, 2 of which recurred after the operation and were then again successfully restored to normal rhythm (Cases 29 and 63). Six patients received their treatment in periods of four months to four years after operation (Cases 42, 43, 44, 45, 46 and 52).

Unsuccessful Cases. The onset of toxic symptoms from administration of quinidin, which for the most part consisted of nausea, fullness of the head, or diarrhea, took place about the same time as the return to normal rhythm. Variable amounts of the drug produced toxic symptoms in those cases which were unsuccessfully treated. Often smaller doses produced toxic symptoms in those who were successfully treated than in those who were not. It does not appear, therefore, that intolerance for the drug can be the cause of failure. Coincident heart disease played the biggest factor as the cause of failure, Case 18 being the only unsuccessful case which we felt was free from cardiovascular disease. When first seen, the patient showed recurrent hyperthyroidism, which was controlled with iodin for six months, after which the iodin effect became less and less apparent and the patient began to lose weight and become clinically more toxic as her basal metabolic rate increased. Quinidin was used without effect during the remission, and again after removal of the thyroid remnant, although given to the point of tolerance. At this writing, nine months after operation, the pulse is still irregular, although the patient is free from toxic symptoms. This patient, as well as all the others in the unsuccessful group, had been digitalized before quinidin administration.

TABLE II.—ESTABLISHED AURICULAR FIBRILLATION STOPPED SPONTANEOUSLY.

Case No.	Diagnosis.	Surgery.	Congestive heart failure on admission.	Digitalized 1½ grains per 10 lbs. of body weight.	Time of cessation.
1	Primary hyperthyroidism	+	○	○	Thirty-six hours postoperative.
2	Adenomatous goiter hyperthyroidism	+	○	○	? Twenty-four hours postoperative.
3	Primary hyperthyroidism	+	○	○	Two days before operation.
4	Primary hyperthyroidism	+	+	○	Two hours postoperative.
5	Primary hyperthyroidism	+	○	+	After rest iodin before operation.
6	Primary hyperthyroidism	+	+	○	After first-stage operation while at home.
7	Primary hyperthyroidism	+	○	○	One hour after operation.

TABLE III.—CASES WHERE QUINIDIN WAS NOT GIVEN.

Case No.	Diagnosis.	Surgery.	Congestive heart failure on admission.	Digitalized 1½ grains per 10 lbs. body weight.	Reason quinidin not given and subsequent course.
8	Adenomatous goiter; hyperthyroidism; hypertension; luetic aortitis	+	+	+	Slow pulse before digitalis and Lugol's, long duration marked congestion; dying one year later.
9	Primary hyperthyroidism; arteriosclerosis; diabetes; hypertension 230/110	+	○	+	Long duration; slow pulse; might have tried later; died six months later.
10	Primary hyperthyroidism; arteriosclerotic heart	+	+	+	Slow large heart, feeble pulsations; long duration; feared embolus.
11	Mitral stenosis; large nontoxic; goiter	+	○	+	Mitral stenosis; developed emboli following digitalization after operation seven days; hemiplegia—one year.
12	Primary hyperthyroidism	○	○	+	Died; broncho-pneumonia; no operation.
13	Arteriosclerosis; primary hyperthyroidism (long standing)	○	○	○	Multiple emboli; died, pneumonia; no operation.
14	M. C. A. goiter; arteriosclerosis; chronic nephritis	○	○	○	Hemiplegia; died one month later; no opertion.

TABLE IV.—UNSUCCESSFUL CASES.

Case No.	Diagnosis.	Surgery.	Congestive failure on admission.	Digitalis given 1½ gr. per 10 lbs. body weight.	Time of quinidin administration, days.	Dose of quinidin, grains.	Follow-up time.	Reaction.
15	Primary hyperthyroidism; rheumatic heart	+	+	+	6 P. O.*	12	Auricular fibrillation one year later	○
16	Primary hyperthyroidism; arteriosclerotic heart, colitis	+	+	+	First stage, 16 P. O.	9	Auricular fibrillation one year later	Severe diarrhea.
					Second stage, 7 P. O.	18		Severe diarrhea.
17	Mitral stenosis; adenomatous goiter	+	○	+	7 P. O.	21	Embolus one month later on digitalis	Nausea.
18	Recurrent hyperthyroidism; irregular pulse since first operation elsewhere four years before	+	○	..	2 mos. A. O.†	21	○	Fullness of head, nausea.
							○	○
		..	..	+	4 P. O.	18	Nine months	Nausea.
					5 P. O.	21	Auricular fibrillation	Nausea.
					6 P. O.	36	Nontoxic	Nausea.
19	Primary hyperthyroidism; hypertension 210/110	+	○	+	3 mos. P. O.	27	....	Nausea.
					6 P. O.	9	Irregular six weeks	

* After operation. † Before operation.

TABLE V.—RECURRENCES.

Case No.	Diagnosis.	Surgery.	Congestive failure on admission.	Digitalis given 1½ gr. per 10 lbs. body weight.	Time of quinidin administration, days.	Dose of quinidin grains.	Result and follow-up time.	Reaction.
20	Primary hyperthyroidism	+	○	+	First stage, 7 P. O.	21	Regular recurred after second operation	Slight fullness of head.
					Second stage, 6 P. O.	6	Irregular; ? regular three months	Nausea.
21	Primary hyperthyroidism; arteriosclerotic heart disease; ? rheumatic	+	+	+	7 P. O.	12	Regular six months, recurred on taking too much thyroxin	Slight nausea.
	Postoperative myxedema	..	..	..	9 mos.	27	Regular six months, thyroxin reduced	None.
22	Adenomatous goiter	..	..	..	1 A. O.	39	Regular	
	Hypertension	+	○	○	2 A. O.	39		
					3 A. O.	39	Recurred when seen six months	Syncope.
					4 A. O.	39		
					1 P. O.	39		
					2 P. O.	39		
23	Primary hyperthyroidism					21	Irregular	
	Hypertension, 200/130	+	+	+	4 P. O.	3 t. i. d. 1 mo.	Regular for three months then recurred	

TABLE VI.—CASES SUCCESSFULLY TREATED.

Case No.	Diagnosis.	Surgery.	Congestive failure on admission.	Digitalis given 1½ gr. per 10 lbs. body weight.	Time of quinidin administration, days.	Dose of quinidin, grains.	Result.	Reaction.	Follow-up time in months, regular.
24	Primary hyperthyroidism	+	+	+	6 P. O.*	30	Regular	○	15
25	Primary hyperthyroidism§	2 stages	+	+	First stage‡	0	Irregular		
					Second stage				
					1½ P. O.	6	Regular, recurred	○	
					2½ P. O.	21	Regular	○	
					Daily dose one month	6	.....	○	12
26	Primary hyperthyroidism	+	○	○	7 A. O.†	26	Regular	○	12
					4 P. O.	15	Regular, recurred	Nausea	
27	Primary hyperthyroidism	+	+	+	6 P. O.	9 t. i. d.	Regular	○	12
28	Primary hyperthyroidism	+	○	○	7 P. O.	21	Regular	Nausea	12
29	Primary hyperthyroidism	+	○	○	3 A. O.	15	Regular, recurred P. O.	Fullness of head	12
					3 P. O.	15	Regular	○	
30	Primary hyperthyroidism; rheumatic heart	+	○	+	6 P. O.	27	Regular	Nausea	15
31	Primary hyperthyroidism	+	○	○	3 P. O.	27	Irregular	○	
					4 P. O.	24	Irregular	○	
				+	5 P. O.	..	Irregular		
					6 P. O.	6	.....	Nausea	
					Daily dose to 11 P. O.	9	Regular	○	12
32	Primary hyperthyroidism	2 stages	○	○	4 P. O. first stage	24	Regular	○	11
33	Primary hyperthyroidism	2 stages	○	○	First stage	0	Irregular		
					Second stage 5 P. O.	15	Regular	○	13
34	Primary hyperthyroidism	+	+	+	10 P. O.	15	Regular	○	12
35	Adenomatous goiter; hyperthyroidism	+	○	○	5 P. O.	39	Regular	○	6 mail report.
36	Adenomatous goiter; hyperthyroidism	+	○	○	5 P. O.	27	Regular	○	11
38	Malignant adenoma; rheumatic heart; mild hyperthyroidism	+	○	Partially +	4 P. O.	33	Regular	○	6
39	Primary hyperthyroidism	2 stages	○	+	First stage	○	Irregular	○	
					Second stage	33	Regular	Fullness of head	12
40	Primary hyperthyroidism	+	○	+	7 P. O.	27	Irregular	Nausea	
41	Primary hyperthyroidism	+	○	○	8 P. O.	12	Regular	○	7
					7 A. O.	15	Regular	○	9
42	Primary hyperthyroidism, operated four years before, nontoxic	○	○	○	4 years P. O.	21	Regular	○	10
43	Primary hyperthyroidism,	○	○	○					

39	Primary hyperthyroidism	2 stages	○	○	Second stage	33	Regular	Nausea	
40	Primary hyperthyroidism	+	○	+	7 P. O.	27	Irregular	○	7
					8 P. O.	12	Regular	○	9
41	Primary hyperthyroidism	+	○	○	7 A. O.	15	Regular		
42	Primary hyperthyroidism, operated four years before, nontoxic	○	○	○	4 years P. O.	21	Regular	○	10
43	Primary hyperthyroidism, operated three and a half years before, nontoxic; blood pressure, 200/100	○	○	○	3½ yrs. P. O.	27	Regular	○	4
44	Primary hyperthyroidism, operated two years before, nontoxic	○	○	+	2 yrs. P. O.	27	Regular	○	Not seen.
45	Primary hyperthyroidism, operated one year before, nontoxic	○	○	○	1 yr. P. O.	33	Regular	Nausea	12
46	Primary hyperthyroidism, operated one year before, nontoxic; blood pressure, 220/80	○	+	○	1 yr. P. O.	39	Regular	Nausea	12
47	Primary hyperthyroidism	+	○	○	8 P. O.	12	Regular	○	12
48	Primary hyperthyroidism; rheumatic heart	+	+	○	5 P. O.	12	Irregular	Nausea	
					7 P. O.	18	Irregular	○	
					Daily dose one month	9	Regular	.....	3
49	Primary hyperthyroidism	+	○	+	4 P. O.	27	Irregular	Nausea	
					3 P. O.	9	Regular, recurred	○	
					6 P. O.	27	Irregular	○	
					7 P. O.	36	Irregular	○	
					8 P. O.	24	Irregular	Nausea	
					9 P. O.	18	Irregular	○	
					Daily dose one month	9	Regular	○	9
50	Primary hyperthyroidism	+	+	+	7 P. O.	21	Regular	○	6
51	Adenomatous goiter; hyperthyroidism; diabetes; blood pressure, 200/120	+	+	+	5 P. O.	12	Regular	○	12
52	Primary hyperthyroidism	+	+	+	120 P. O.	24	Regular, recurred	○	12
					121 P. O.	24	Regular		
53	Recurrent				7 A. O.	18	Regular, recurred P. O.		
	Primary hyperthyroidism	+	○	○	7 P. O.	18	Regular	○	12
54	Primary hyperthyroidism	2 stages	○	○	First stage, 4 P. O.	21	Regular		
					Second stage	○	Irregular few hours	.....	12
55	Primary hyperthyroidism	2 stages	○	○	First stage	..	Irregular		
					Second stage 6 P. O.	33	Regular	○	
					Daily dose one month	6	.....	.....	12

* After operation
† Before operation.

‡ Six weeks elapsed between first and second stage of operation.
§ Primary hyperthyroidism (exophthalmic goiter).

Successful Cases. The majority of the 31 patients in this group had their irregularity converted to normal rhythm usually on first attempt with moderate doses of the drug. Sixteen were under the influence of digitalis, while the remainder, 15 were not given the latter drug. Ten patients of this group showed congestive heart failure on admission. In all these cases there was vigorous heart action, and an increased pulse pressure. Congestive failure was easily controlled by rest, iodin, and, in all but one case, digitalis. Attempts to restore normal rhythm were not begun until the third day after operation, in most instances from the fifth to the seventh day. This gave the maximum time to await spontaneous return to normal rhythm without holding the patient unnecessarily in the hospital, and at the same time allowed for the maximum subsidence of toxicity while under our observation. The irregularity of the pulse stopped in all cases during quinidin administration, so that it seems beyond a reasonable doubt that quinidin was responsible for this.

Reactions. Nausea was produced in 21 cases, while "fullness of the head" was complained of by 3 others. Diarrhea occurred in 2 cases, while diffuse punctate skin eruption was seen in another. One patient (Case 22) had a severe reaction following larger doses than we had previously given. After such a reaction, one hesitates to prescribe as large doses as were used by Sidel and Dorwart.[7] Although we are not certain that quinidin was the cause of the reaction, we are reporting this case in detail.

Case Report. The patient, an unmarried woman, aged sixty-two years, came to the Clinic complaining of a goiter, which she had had for twenty years. There was no definite history of thyroid toxicity, although three years before she had had a nervous breakdown and was confined to bed for a month.

The general physical examination was negative except for the following findings: There was a very slight cyanosis of the lips. Emphysematous breath sounds heard throughout the chest, with a few crackling râles at both lung bases. The blood pressure was 150 systolic and 100 diastolic, the heart was only slightly enlarged, showing no murmurs, but auricular fibrillation was present, with an apical rate of 120. There was no edema.

An adenoma about the size of an orange and almost entirely subclavicular was found in the thyroid gland. Roentgen ray plates showed the trachea deviated to the right, with moderate anteroposterior pressure on the latter structure. The basal metabolic rate was +14 per cent.

Quinidin was begun the day after admission and 156 grains were given in four days' time, with no toxic symptoms. The pulse slowed down, but did not become regular. Five days after admission the adenoma was removed without incident. Seven days after operation, the pulse still irregular, quinidin was given again, 39 grains daily for two days. On the evening of the second day, the nurse reported that the patient suddenly fell back in bed unconscious. She was slightly cyanotic, rolled her eyes, but in a few minutes returned to consciousness. The pulse was not noted.

The next day the patient received 6 grains of quinidin early in the morning. That evening when the patient was visited by one of the surgical

service, another attack occurred. The following is the note recorded at the time:

"This evening the patient was seen at 5.15. Her lips were slightly cyanotic, pulse rate was 60 and irregular and was the slowest it had been at any time. Immediately on leaving the room, the patient clutched the region of her heart with her right hand and fell backward in bed. There was an immediate loss of consciousness, but no twitchings or convulsions. There was rapidly deepening cyanosis. The pulse was not felt and auscultation failed to show any signs of the heart beat in any position. She then made convulsive efforts at breathing with apparent obstruction, but when the dressing was removed there was no evidence of the latter. The tongue was not obstructing and was pulled forward without effect. She breathed four times during the two minutes, during which there was apparently cessation of the heart beat. While oxygen and caffein were being prepared at the end of the two minutes, the heart sounds reappeared with immediate resumption of the pulse. Her color changed shortly to a rosy red cyanosis, thence to brighter red. The mouth dropped on the left and sagged open. The pupils during the entire time were markedly dilated and the eyes glazed. With the resumption of the heart beat, there was diffuse sweating. The patient made movements of her head and after a few minutes uttered groans. Unconsciousness persisted and, on account of extreme restlessness, codein was given subcutaneously. The heart was fibrillating at a rate of 80 to 100 at this time. Consciousness returned after about an hour and a half."

The next morning the pulse was regular and electrocardiographic tracing revealed normal rhythm at a rate of 42. No further attacks occurred and the patient left the hospital soon after, feeling perfectly well. The pulse remained regular for some time, but when seen six months later, auricular fibrillation had recurred. Whether or not this was due to toxic action of the drug on the respiratory center, or whether it was due to ventricular fibrillation with cerebral anemia, is impossible to say.

Kerr and Bender[8] report a case of syncope similar to this one in which they were able to obtain electrocardiographic tracing which showed ventricular fibrillation.

An increase in the apical rate during administration of the drug was frequently seen in other patients. This follows a slowing of the auricular rate as observed by Lewis and others.[9] They state that if digitalis is given first, the increase in ventricular rate will be less and, therefore, less disturbing to the patient. We have not found this procedure necessary.

Method of Dosage. In most instances we have used the daily plan of dosage which we have previously described,[5] similar to that advocated by Smith and Clark.[11] The order for treatment is written as follows:

℞: quinidin sulphate grains three after breakfast.

If no reaction or unpleasant symptoms develop, give 6 grains with one-half glass or more of fluid every two hours until the pulse is regular, unpleasant symptoms arise, or not more than a total of 39 grains has been given.

We have found this to be satisfactory in hospital treatment and in a few cases treated at home. Because of the rapid absorption of

quinidin, we have not found it necessary to wait longer than two hours for manifestations of an idiosyncrasy to the drug. When this plan of treatment has been ineffectual, or when toxic symptoms have occurred before the heart has become regular, our next step has been to give 6 or 9 grains after each meal for several days. This may be tolerated by the patient and, if continued, may prove successful (Cases 21, 27 and 40). If no results are obtained by this procedure, the patient is then discharged with instructions to take 3 grains after each meal until his return to the Clinic. In cases where there has been some difficulty in establishing normal rhythm, we have prescribed a daily dose of 6 grains, to be continued for a month or two in order to insure permanency of the result.

Recurrences. Recurrences have been few. One patient (Case 21) entered with mild congestive failure. He showed auricular fibrillation, an old mitral lesion and arteriosclerosis. After operation the normal rhythm was restored with 9 grains of quinidin. Three months later he had developed postoperative myxedema. He was given thyroxin and when seen three months later, was again fibrillating. Clinically, as well as by the basal metabolic rate, it was evident that he was taking too much thyroxin. Quinidin was again used successfully (27 grains) and the thyroxin reduced. Six months later when seen, his pulse was regular. Another patient (Case 20) was successfully given quinidin after the first stage operation. But auricular fibrillation recurred following the second stage. Quinidin was again used, but the patient developed severe diarrhea. The patient's pulse was still irregular at the end of three months, at which time we prescribed 3 grains of quinidin to be taken after each meal. Two months later the patient reported by mail that her pulse is regular, although we cannot be sure of this until we see her again. The third case which recurred (Case 22, discussed above) did not, in our opinion, have auricular fibrillation because of hyperthyroidism. She had distinct hypertension. She was not given quinidin again because of the severe reaction described above. The fourth patient had hyperthyroidism and a coincident hypertension (Case 23). Although successfully treated at first, auricular fibrillation recurred after six months. From these experiences, we feel that recurrence of auricular fibrillation in goiter patients are usually due either to recurrence of thyroid toxicity or to coincident cardiovascular disease.

Summary. Fifty-nine cases of postoperative paroxysmal auricular fibrillation in thyroid patients have been studied to compare the relative efficacy of digitalis and quinidin. While digitalis will slow the pulse, we do not believe that it exerts a favorable action on the stopping of the paroxysms. Quinidin, in our hands, has proved successful in all cases of this type. Fifty-three cases of established auricular fibrillation, associated with goiter, have been presented

showing the clinical types met with, the selection of cases with quinidin and the results of those treated. In selected cases, quinidin has been permanently successful in 88 per cent of those treated with the drug. Iodin and thyroidectomy caused cessation in 15 per cent of all operated cases during the period of hospital observation. Iodin, thyroidectomy and quinidin resulted in a permanent return to normal rhythm in 76 per cent of all operable cases, at least for the time over which we have observed them. In hyperthyroidism uncomplicated by cardiovascular disease, return to normal rhythm may be anticipated in practically 100 per cent of cases.

Conclusions. 1. Quinidin is the most effective drug in the treatment of postoperative paroxysmal auricular fibrillation.

2. Quinidin is the ideal drug for restoration of normal rhythm from established auricular fibrillation in selected cases of hyperthyroidism.

3. The plan of two hourly dosage is practical, no more dangerous in our hands than other methods, and is valuable as a time saver.

NOTE.—Since the paper was written, we have been successful in having 48 patients return for examination who had had established auricular fibrillation at the time of their operation from two to seven years before. Quinidin had not been given to this group. Twenty-five (52 per cent) of these patients showed normal rhythm, the same as the per cent reported by Phillips and Anderson.

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THE ABSORPTION OF GLUCOSE PER RECTUM.

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The administration of glucose per rectum is a widely used procedure. Yet few generally accepted modes of therapy have had so little control study. Observations on blood sugar changes following the injection of rectal glucose have been made by Varela and Rubino,[1,2] Tallerman,[3] Levi[4] and others. For the most part, results obtained strongly indicate that no marked rise in blood sugar level occurs, but on the contrary there results an actual lowering, without preliminary hyperglycemia.

Levi's[4] work on diabetics is particularly enlightening. He finds in 8 cases of diabetes mellitus that after giving 50 to 80 gm. of dextrose rectally there occurs an average rise of only 11 mg. at one-half hour, followed by a sharp and rapid drop in blood sugar values, the level after two hours being 29 mg. below the fasting figure (209 to 180). Four of his 8 cases showed no rise during any period of the observation. These findings in diabetics are particularly significant since at the high blood sugar levels which existed, the amount of the rise did not exceed experimental limits of error of the method, and it is well known that any appreciable absorption of sugar will be reflected in the diabetic.

This drop in blood sugar occurring in the normal is in all probability a manifestation of postalimentary hypoglycemia, despite the fact that no preliminary rise has taken place. Following the introduction of even very small quantities of glucose into the blood stream, whether directly or by absorption from the intestinal tract, a change takes place whereby metabolism of glucose occurs more rapidly than under fasting conditions and hypoglycemia results. As Jordan[8] has proven, this change is a hyperinsulinism due to stimulation of the islands of Langerhans by the hormone action of the absorbed glucose.

The drop in blood sugar after administering glucose rectally is not, therefore, dependent upon complete absorption having taken place or a preliminary hyperglycemia, but can occur after trivial amounts of glucose have been absorbed, and with the bulk of the glucose enema remaining in the lumen of the bowel, since we know from Jordan's[8] experiments, that quantities of absorbed glucose too small to be reflected in the urinary output of sugar still have the power of stimulating insulin production. Other evidence tending to indicate that postalimentary hypoglycemia is not dependent upon

complete absorption, is at hand. Cajori, Crouter and Pemberton[6] quote the work of Foster, and DuVigneaud and Karr[7] support the observations of Johansson, MacLean, DeWesselow and others, who have shown that during the hypoglycemia following a preliminary rise, second doses of glucose result in no further rise of the blood sugar level. Jordan[8] points out the work of Thalheimer, Raine, Perry and Buttles, who injected glucose into the veins of dogs continuously over a period of two hours and observed that while a rise in blood sugar took place during the first hour, the blood sugar level actually fell during the second hour, and when the injection was stopped, an extremely rapid drop took place, resulting in severe symptoms like those of insulin shock. It is conceivable therefore, that the hypoglycemia which is believed to follow rectal administration of sugar, can take place, even though a large part of the glucose introduced still remains within the lumen of the rectum.

It has already been pointed out that Levi[4] found no significant rise in blood sugar levels in diabetics given glucose by rectum. Luthje (quoted by Carpenter[5]) conducted further experiments on diabetics and was able to demonstrate that while small doses of glucose by mouth resulted in increased urinary sugar output, no such rise followed the administration of 100 gm. by rectum, but on the contrary, the rate of sugar elimination actually fell. In the light of these experiments, it is not conceivable that any considerable absorption of sugar had taken place.

Carpenter,[5] however, has demonstrated that when patients are given glucose by rectum, there is a distinct shift toward a carbohydrate metabolism level, indicating that under these conditions a higher proportion of sugar is burned than in the normal fasting individual. This phenomenon does not necessarily mean that any great quantity of glucose has been absorbed. Under the conditions of his experiment we have no means of knowing whether the shift represents utilization of sugar equivalent in amount to that absorbed, or whether sugars previously stored in the body have been burned in excess, as the result of stimulation to carbohydrate metabolism resulting from the hormone action of a relatively small amount absorbed. In either case, changes in respiratory quotient would be the same. If the latter be true and sugar is burned in excess of that actually absorbed, we should find some indication of a depletion of the sugars previously stored, and such evidence is, in fact, suggested in the form of the lowered blood sugar level reported found after rectal administration of solutions of glucose. We must, therefore, not be too hasty to accept the change in respiratory quotient as indicating the absorption of large amounts of sugar, for in all probability the increased carbohydrate metabolism takes place to a greater degree than can be accounted for by the utilization of absorbed glucose *per se*. Only by this explanation can we account for the lowering of the blood sugar occurring without a preliminary

rise, for it is apparent that stored sugars are being burned more rapidly than they can be replaced by the relatively slow rectal absorption.

If the drop in blood sugar is greater than occurs from the normal utilization of sugar during a fasting period, and no preliminary rise has taken place, it is obvious that glucose is being burned more rapidly than it is absorbed, which is important in view of the fact that glucose is usually given per rectum only in those cases where sugar depletion is already present or likely to occur. The status of sugar deficiency would then be aggravated rather than improved by the instillation of sugar *via* the rectal route.

There is no positive evidence in the literature to indicate the ultimate fate of all the glucose introduced in this fashion. A large part of it can be recovered in the stools many hours after the instillation. Carpenter[5] points out the following experiments: Zemisch, in 1905, recovered 32 per cent of 150 gm., injected over a two-day period. Heile found a return in the stool of 94 per cent and in a second exepriment 75 per cent after one hour. Varela and Rubino[1] recovered 60 per cent but do not give the details of recovery. Many other similar results are reported.

If glucose does remain in the bowel for long periods and in large quantities, we must consider what part is lost by way of fermentation as the result of bacterial action of the intestinal flora. To determine this, Bingel (quoted by Carpenter[5]) fermented glucose with feces and found a disappearance of 34 per cent and 28 per cent of the planted glucose after five hours of incubation.

No experiments have been reported to indicate that the drop in blood sugar level which has been found following rectal administration of glucose exceeds the drop during a similar fasting period without the introduction of sugar, nor have comparisons been made to demonstrate the blood sugar reactions in the same patient when glucose is given by mouth and by rectum under otherwise similar conditions. The scope of this paper is to indicate what changes in blood sugar take place when sugar is introduced per rectum, to compare these changes with those following the introduction of equal quantities of glucose by mouth, and to point out how these variations differ from blood sugar level curves during a similar fasting period when no glucose is introduced.

Determinations of the sugar residue of the stools of patients whose blood sugar curves are reported will be given in order to demonstrate the actual quantities of glucose remaining in the bowel several hours after its administration, and experiments will be described to point out the rate of destruction of glucose from fermentation due to the action of the bacterial flora of the intestinal tract.

Method. Bearing in mind the observations of Rubino and Varela[2] and the conclusion of Carpenter[5] that "the higher the

concentration of the solution or the higher the weight of glucose actually introduced, the greater is the absorption," we used in each case, a 33 per cent solution of C.P. dextrose, made up with 80 gm. of the sugar in 240 cc. of plain tap water, at body temperature.

Patients were males in middle life without colonic or metabolic diseases, for the most part being treated for minor injuries. Following the ordinary hospital meal at 5.30 P.M. the previous evening, subjects were starved for fourteen hours. The following morning a cleansing soap-suds enema was given. An hour later a fasting blood sugar was taken, all blood specimens being preserved in sodium fluoride, and then 240 cc. of the 33 per cent dextrose solution introduced with an ordinary soft rubber rectal tube passed into the ampulla. Instillation was over a ten-minute period. Patients were kept entirely at bed rest, and the glucose enema retained throughout the length of the experiment (four hours). Blood specimens were taken just before the glucose was introduced and forty-five minutes, one and a half hours, three hours, and four hours afterward, and analyzed immediately after the taking of the last specimen.

The following morning upon the same patients after a similar fasting period, a fasting blood sugar was taken, 80 gm. of C.P. dextrose in about 350 cc. of water flavored with orange and lemon were given by mouth, and blood sugars taken after one-half hour, one hour and two hours, in order to obtain a basis of comparison for the changes occurring after rectal administration.

As a control, two normal patients were treated as the others who had been given the glucose by rectum, except that a 5 per cent salt solution was substituted for the 33 per cent glucose, and blood taken at intervals over a four-hour period, and analyzed for sugar.

All of the patients given the rectal instillations suffered some discomfort, usually moderate, but only one was forced to pass the enema before the end of the experiment.

Blood sugar analyses were by the Folin-Wu method and performed through the courtesy of Dr. A. H. Zeiler by the laboratory of Drs. Brem, Zeiler, Hammack and Maner, Los Angeles.

The changes in blood sugar occurring in a normal individual between the fourteenth and eighteenth hours of a fast period, are indicated by those of our patients who received saline by rectum, and the results are in keeping with those reported by Varela and Rubino[2] who, however, present no actual figures. Our results are tabulated in Table I. The average fasting level after fourteen hours is 90 mg. per 100 cc. with a very slow, steady, gradual decline to 86 at the end of the eighteenth hour, a drop of only 4 mg. during this four-hour period.

Results obtained after the rectal injection of 80 gm. of C.P. glucose in 240 cc. of water as described above, are given in Table II. They are presented together with the blood sugar readings of these same patients after an equal quantity of glucose had been given by mouth.

TABLE I.—CHANGES IN BLOOD SUGAR IN MILLIGRAMS OCCURRING BETWEEN THE FOURTEENTH AND EIGHTEENTH HOUR OF A FASTING PERIOD.

	Fasting.	¾ hr.	1½ hrs.	3 hrs.	4 hrs.
Patient 1 . . .	84	80.0	85.0	84	80
Patient 2 . . .	96	95.0	94.0	90	92
Average . .	90	87.5	89.5	87	86

Two hundred and fifty cubic centimeters of 5 per cent saline solution introduced after fasting sugar was taken.

TABLE II.—CHANGES IN BLOOD SUGAR IN MILLIGRAMS FOLLOWING ADMINISTRATION OF 80 GM. OF GLUCOSE.

	Route.	Fasting.	¼ hr.	½ hr.	1 hr.	½ hrs.	2 hrs.	3 hrs.	4 hrs.	Maximum change.
Patient 1	M	103	166	..	167	..	142	..	..	+64
	R	122	..	118	..	111	..	108	103	−19
Patient 2	M									
	R	101	...	101	...	103	Enema expelled			
Patient 3	M		Glucose by mouth refused							
	R	108	..	126	..	105	..	109	93	+18
Patient 4	M	105	216	..	222	..	162	..	..	+117
	R	100	..	88	..	87	..	86	90	−14
Patient 5	M	123	150	..	162	..	138	..	..	+39
	R	119	..	101	..	99	..	89	100	−30
Patient 6	M	111	140	..	184	..	152	..	..	+73
	R	104	..	91	..	93	..	86	85	19
Patient 7	M	115	158	..	148	..	144	..	..	+43
	R	86	..	95	..	92	..	92	87	+9
Average	M	111	166	..	176	..	146	..	..	+65
	R	106	..	103	..	99	..	94	92	−14

M—80 grams of sugar in 350 cc. of water, by mouth.
R—80 grams of sugar in 250 cc. of water, by rectum.

The sugar curves after oral administration are reasonably typical of the accepted normal. In those cases (Patients 4 and 6) in which the blood sugar level exceeded 180 mg. the urine was positive for sugar by Benedict's test, at the height of the curve. All other urine specimens were negative for sugar.

The curves following rectal administration require more careful analysis. In only 2 of the 7 patients was there any rise. Patients 3, an excitable Mexican, presented an initial rise of 18 mg. which dropped to fasting level at the end of one and a half hours. Patient 7 presented an initial rise of 8 mg. (as compared with an initial

rise of 43 mg. when glucose was given by mouth) and then a steady decline to fasting figures. The remaining subjects each showed an actual drop in blood sugar readings, the greatest being a decrease of 30 mg. (Patient 5), at the end of three hours.

Throughout the length of the experiment, except for the two exceptions already noted, the average drop in blood sugar was constant and steady without rises at any time. The average curve of our series of cases, when plotted, is practically a straight line, gradually dropping off from the high fasting level to the lower figure at the end of the experiment. This demonstrates that the drop in blood sugar values takes place in a steady progression from one hour to the next, the average level at the end of four hours being 14 mg. below fasting, as compared with a drop of only 4 mg. when no glucose was introduced into the body. In other words, the drop in blood sugar level is three and one-half times as great when sugar in these quantities is instilled into the rectum, than when no sugar is introduced.

After the final blood sugar had been taken, the first stool passed was recovered without rectal washings of any kind, and analyzed for its sugar content. Analyses were by the Folin-Wu method. No difficulty in technique was encountered for the stools were all watery and relatively clear.* One patient retained the sugar enema for seven hours. In this latter case, specimens were examined after seven, ten and thirteen hours, the first analysis yielding 26.2 gm., the second 1.9 gm., and the third after thirteen hours, less than 1 gm. of the 80 gm. introduced. Results are indicated in Table III.

The two latter figures do not appear in the table.

TABLE III.—RECOVERY OF GLUCOSE FROM STOOL: 80 GM. INTRODUCED.

Patient.	1.	2.	3.	4.	5.	6.	Average.
Hours after introduction	7.0	4.0	4	4.0	4.0	3.0	4.3
Grams recovered . .	21.0	10.0	16	33.6	10.0	25.0	19.2
Percentage recovered .	26.2	12.5	20	42.0	12.5	31.2	24.0

From these studies it is apparent that four hours after the injection of 80 gm. of glucose per rectum, an average of 24 per cent of this amount could not conceivably have been absorbed for it still remained in the lumen of the rectum and was returned in the stool. In one case 26.2 per cent was recovered after seven hours.

Fermentation experiments to determine the rapidity with which glucose is destroyed by the fermentative action of the intestinal flora were carried out. Glucose, feces and water were combined so that the quantities of glucose were 5 per cent and 3 per cent respectively, the quantity of stool constituting roughly 40 to 50

* To determine the accuracy of our analysis of the sugar content of stools, sugar in known amount was added to a stool, and the mass analyzed for sugar. (Dr. A. H. Zeiler.) In no case did an error of more than 0.3 per cent occur.

per cent, the mass totaling about 100 gm. At the end of seven hours of incubation, analysis by the picramic method revealed that only 0.5 per cent of glucose in the first case and 0.4 per cent in the second experiment remained. Other specimens were taken at ten and thirteen hours and resulted in a further drop of about 0.1 per cent at these times. (Brem, Zeiler, Hammack and Maner Laboratories.) The masses were filled with bubbles of gas and much fermentation had taken place. The figures obtained demonstrate that approximately 90 per cent of the planted glucose had been destroyed after seven hours.

This observation, coupled with the fact that 25 per cent or more of injected glucose remains in the bowel for a period comparable to the elapsed time before the first analyses of the fermentation experiments were made, strongly indicates that much of the sugar we have introduced remains in the intestinal tract and undergoes fermentation, rather than becoming available to the body for metabolic purposes.

Discussion. There can be no question but that a small part of a quantity of glucose introduced per rectum is absorbed and acts as a stimulant to insulin production, destroying larger amounts of sugar previously stored. This assumption is necessary to account for the increase in sugar metabolism which takes place as evidenced by the rise in respiratory quotient and the lowering of blood sugar. That the amount absorbed is not great can be deduced from the observation that no rise in blood sugar and no increase in sugar elimination takes place even in the sugar sensitive diabetic. By comparing our figures with those in the literature it is obvious that the concentration and period of time devoted to the instillation are not factors in the ultimate result nor can it be argued that nearly complete absorption does take place, but too slowly to be reflected by a rise in blood sugar for Staube (quoted by Carpenter[5]) has shown that repeated feedings by mouth of very small quantities of glucose, results in an increase of the sugar content of the blood.

From the evidence at hand, we are not free to draw definite conclusions concerning the therapeutic value of glucose by rectum; but this must be left for observations upon the reactions of patients having definite need for glucose.

When we consider that the ordinary Murphy drip or small repeated enemata given in the usual fashion introduces over a twenty-four-hour period only 75 to 150 gm., equivalent to 300 to 600 calories, and that much of this is lost by nonabsorption and passed out in subsequent stools, and that fermentation destroys another very appreciable quantity, we must realize, even without looking further into the problem, that the rectal administration of sugar is not a satisfactory therapeutic procedure in that it fails in its intended

purpose of making available to the organism an appreciable quantity of utilizable sugar.

Summary. Seven fasting patients were given 80 gm. of glucose by rectum and on the next day an equal quantity by mouth. Blood was analyzed at intervals for sugar content and it was found that when glucose was given by mouth an average maximum rise of 65 mg. per 100 cc. of blood took place. Following rectal administration no such rise resulted, but on the contrary the average blood sugar level fell after four hours, from 106 to 92, a drop of 14 mg. This compared with a drop of only 4 mg., when, under otherwise similar conditions, saline was substituted for the glucose per rectum. These findings were interpreted as indicating that sufficient absorption had taken place to stimulate insulin production, resulting in an increased metabolism of previously stored sugar, but that the absorption from the rectum had not been sufficiently rapid to replace the body sugars so destroyed.

We have pointed out that the increase in respiratory quotient may be due not to the absorption and ultilization of an equivalent amount of sugar absorbed by the rectum but rather to the metabolism of sugars previously stored, the increased rate of destruction being due to a hyperinsulinism, which results as Jordan[8] has proven when small quantities of glucose are introduced into the body.

The stools of patients given sugar by rectum were analyzed for sugar content, and four hours after introduction as much as 42 per cent (Patient 5) of the introduced glucose was recovered in the stool. The average recovery after four hours was 24 per cent, and in one case 26 per cent was recovered in a single stool seven hours after the introduction of the glucose.

To determine how much fermentation might be expected to take place in the rectum, glucose and feces were combined and incubated for thirteen hours. Specimens examined at seven hours showed that destruction of nearly 90 per cent of the glucose had taken place.

Conclusions. From these observations it can be concluded, that:

1. Following the introduction of glucose into the rectum blood sugar levels fall without a significant preliminary rise.
2. This fall is greater than that occurring during a corresponding fasting period when saline is introduced instead of glucose.
3. The bacterial content of the lower bowel rapidly ferments glucose.
4. Absorption of glucose by the rectum is sufficiently slow to permit fermentation to take place, 25 per cent of the introduced glucose having been recovered in stools four hours after a glucose enema.

NOTE.—The author expresses his appreciation to Dr. A. H. Zeiler for his kind coöperation in carrying out the laboratory procedures, also for many valuable suggestions, and to Drs. Herman Sugarman and Wayland Morrison for the use of clinical material on their wards.

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PRESSURE AS A FACTOR IN THE DEVELOPMENT OF NEURITIS OF THE ULNAR AND COMMON PERONEAL NERVES IN BEDRIDDEN PATIENTS.*

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Neuritis not uncommonly develops in patients who are on the highway to recovery from prolonged and severe illnesses. It is often alarming to the patient, and because of its persistence soon proves to be disturbing to the physician. The surprising frequency with which only the ulnar or common peroneal nerves may be involved stimulates one's interest. Neuritis usually has a toxic or infectious basis, and the toxic or infectious agents often possess canny specificity in their choice of nerves (for example, neuritis in the upper extremities due to lead and neuritis in the lower extremities due to arsenic). Therefore, the inviting explanation that the cause of the forms of neuritis under discussion is toxicity or infection has been the one generally accepted. Singer, who has contributed an excellent monograph on disorders of the ulnar nerve, evidently was not altogether satisfied with this explanation. He advanced the view that the highly organized segmental function subserved by the ulnar nerve may account for its ready vulnerability.

The unprotected situation of the ulnar nerve at the internal condyle and of the peroneal nerve at the neck of the fibula, and the closeness of these nerves to bony structures must be potential sources of danger. The observation of a number of cases of paralysis

* Submitted for publication, July 26, 1929.

of these nerves, as they developed in prostrated patients, has led me to the belief that compression is a factor of greater importance than is generally granted.

Cases Illustrative of Disturbance of the Ulnar Nerves. CASE I.—A comptroller, aged forty-nine years, had suprapubic pain and dysuria. Examination disclosed carcinoma of the bladder, marked cystitis and moderately high blood pressure. Suprapubic cystostomy was performed and radium was applied to the growth. For a period of two weeks, the patient suffered intense pain, which necessitated frequent administration of morphin; during this time he lost much in weight. When his general condition improved, he complained of numbness and weakness of the hands. On neurologic examination, almost complete motor paralysis and a moderate degree of sensory paralysis in the fields of both ulnar nerves was found; he related that while he had been in agony he had sunk his elbows heavily into the bedding at his sides. When he returned for reëxamination three years later, there was no evidence of recurrence of the carcinoma, and the paralysis and numbness had disappeared completely.

CASE II.—A physician, aged sixty years, had difficulty in passing urine. He had become very ill and had lost 30 pounds in weight. Examination disclosed that the obstruction was due to enlargement of the prostate gland, for the relief of which suprapubic cystostomy was done. After lying in bed on his back for about two weeks, he complained of numbness, limited strictly to the distribution of the ulnar nerves. Objectively, neither weakness nor anesthesia were found.

CASE III.—A housewife, aged forty-eight years, complained of frequent and painful urination and general malaise. The diagnosis was ulcerative cystitis and pyelonephritis. The systolic blood pressure was 200 mm. and the diastolic pressure 104 mm., measured in millimeters of mercury. She had lost 24 pounds in weight. After having lain in bed on her back for a month, she complained of continuous tingling and numbness of the hands. Examination disclosed slight diminution in sensation over the distribution of both ulnar nerves. This disappeared as her general health improved.

CASE IV.—A housewife, aged twenty-nine years, and weighing 93 pounds, said that she had been "run down" all of her life. Before coming to The Mayo Clinic she had spent many months in bed, with her elbows resting on the bed and her hands crossed over her abdomen. Gradually, annoying numbness had developed over the distribution of both ulnar nerves. Examination disclosed mild hypertension, an ovarian cyst which had not produced symptoms, and a basal metabolic rate of −16. The numbness gradually disappeared after the patient had been dislodged from her bed and had been supplied with both physical and mental support.

CASE V.—A laborer, aged sixty-three years, had suddenly lost consciousness and had fallen to the floor, where he had lain for three days. When he had recovered consciousness, he had discovered a bedsore over the sacrum, and weakness and numbness of both hands. Since the onset of his illness he had lost 40 pounds in weight. Examination disclosed bilateral ulnar palsy of moderate degree and evidences of cerebral arteriosclerosis; the latter presumably accounted for the attack of unconsciousness.

Cases Illustrative of Disturbance of the Peroneal Nerves. CASE VI.—A barber, aged forty-one years, over a period of six months had gradually slipped into a state of extreme mental dilapidation, accompanied by symp-

toms and signs of increased intracranial pressure. He had lost greatly in weight and appeared to be moribund. The muscles supplied by the peroneal nerves were moderately paralyzed and sensory tests showed slight impairment in the distributions of these nerves. The normal popliteal concavities had become so obliterated by loss of weight that the upper ends of the fibulas rested hard on the surface of the bed. After the evacuation of a large subdural hematoma, the patient made a rapid recovery from all symptoms.

CASE VII.—In a student, aged seventeen years, bilateral otitis media had developed. He had failed to recover, and during the ensuing months had become so feeble and emaciated that he had been confined to bed. Symptoms of a brain abscess appeared, but localization of it was not possible. At a second exploration, material from a huge abscess was evacuated from the right temporal lobe. He rallied quickly, and it was then discovered that complete bilateral sensory and motor paralysis of the peroneal nerves had developed. In due course of time he recovered completely.

CASE VIII.—A postal clerk, aged fifty-four years, had become very ill with symptoms of exophthalmic goiter. He had been confined to bed for several weeks and had lost 22 pounds in weight. Following thyroidectomy and while he was still in bed, there appeared marked motor and slight sensory paralysis of the left peroneal nerve. When he was last seen there was marked improvement from the paralysis.

CASE IX.—A woman bookkeeper, aged sixty-seven years, had had symptoms of gall stones. Examination disclosed, in addition, a systolic blood pressure of 180 mm. and a diastolic pressure of 90 mm., measured in millimeters of mercury. While the patient was confined to bed following operation, paralysis and numbness of moderate degree appeared in the distribution of the right common peroneal nerve and palsy of slight degree in that of the left. When the patient was last heard from she had recovered completely.

Comment. In these cases, either the ulnar or the peroneal nerves alone were involved; there was no suggestion of peripheral neuritis elsewhere. In all cases but one, the affliction was bilateral. None of these patients had used alcohol. Injury to the ulnar nerve by the edge of the operating table could be excluded in 3 cases of the first group, since an operation had not been performed and on the basis of the history, it was hardly to be considered in the remaining two. There was no evidence of luxation of the nerve, and no deformity of the elbow. Of the 4 patients in the second group, with symptoms referable to the peroneal nerves, 3 were males, resembling in sex incidence that noted in palsy from crossing the legs.[8] A toxic infectious state is usually blamed for the production of neuritis. Infection is ubiquitous and difficult to disprove; in 2 of the 5 cases of ulnar neuritis and in 2 of the 4 cases of peroneal neuritis, infection could not be demonstrated.

Singer stated that complicating ulnar neuritis alone occurs most often with typhoid fever and during the puerperium. It has also been observed that when neuritis complicates typhoid fever, it appears during convalescence. This implies that the patient has been in bed for a long time.

Singer granted that pressure may be a factor in the development of ulnar neuritis in those cases in which the arm is thrown across the bed in such a manner that the nerve is compressed by the hard edge of the bed, or in which the arm is thrown over the head. In the latter case the mechanism is quite different; the nerves probably are pinched between the clavicle and the cervical spine or between the clavicle and the first rib and the plexus rather than the ulnar nerve alone is usually implicated. In Peel's case of ulnar palsy, the patient had slept on her face, with the arm placed under the abdomen to relieve pain. In commenting on ulnar neuritis, Seeligmüller assigned some importance to pressure as a cause. Lloyd was more emphatic; in reporting the case of a patient who had had typhoid fever and in whom, subsequently, ulnar palsy developed, he expressed the opinion that pressure, rather than a toxin, was responsible for such cases of palsy; however, he mentioned that he could not exclude injury by the attendants as a possible factor. Oppenheim stated that pressure may cause ulnar neuritis in emaciated patients who are confined to bed. My experience indicates that pressure on the hard arms of a chair may also contribute to the production of neuritis. The evidence in my cases suggests that the ulnar or peroneal nerves had been compressed between a bone and the underlying surface.

Lüderits, Stopford, and others have observed that in neuritis due to pressure, involvement of motility occurs before sensory disturbance. This was not true in the cases of ulnar palsy in which sensation and motility were involved equally or in which one was affected as often as the other. In the cases of peroneal palsy, however, motility was always more affected than sensation, except in Case VII, in which both were completely paralyzed. Disease of the blood vessels is a factor on which Lapinsky laid great stress in a discussion of the production of senile and arteriosclerotic neuritis, and it is likely that pressure also may interfere with the blood supply to the nerve.

Traction also may produce paralysis of the common peroneal nerve. This was seen in a case of spinal gliosis in which the lesion in the spinal cord had produced such an alteration in tonicity that extreme genu recurvatum had been produced; this resulted in peroneal palsy of peripheral origin. The forcible correction of ankylosis of a knee in flexion also may result in peroneal paralysis. Most of the patients that I have observed, particularly those in whom peroneal neuritis developed, had been extremely ill, and had lost greatly in weight and in muscular tonus. The popliteal recesses had become obliterated and the heads of the fibulas, unduly prominent. Evidently stretching of the ligamentous supports of the knees had taken place so that partial genu recurvatum could occur. This would add the factor of traction.

Summary. Selective paralysis of the ulnar or peroneal nerves not infrequently occurs in bedridden patients. The assumption that the causes of these forms of paralysis are infection or toxicity would seem to be true only in part. Compression of these nerves between the bone and the underlying surface and, in the patients with peroneal palsy, additional traction on the nerve and on the muscles supplied by this nerve, seem to be important but generally neglected factors. Interference with the blood supply to the nerve, and loss in weight, which deprives these nerves still further of their protective coverings, evidently contribute. Preventive measures include massage, attention to the bedding, proper support and position of the limbs, and care that the covers, when they are tucked in, do not draw the feet too tightly downward. Subsequently heat, massage, and mechanical support may be prescribed. Although recovery may be delayed for several months, it may be anticipated.

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A STUDY OF INTESTINAL TUBERCULOSIS AMONG EXSERVICE MEN.*

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Tuberculous infection of the intestines may occur by direct invasion from the lumen, through infection from tuberculous lymph glands, or through the blood stream. There are two clinical forms of intestinal tuberculosis—the secondary or ulcerative type commonly seen in cases of advanced pulmonary tuberculosis, and the primary or hyperplastic type, the latter being more frequently encountered abroad than it is in this country.

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Stewart,[1] as reported by Barrington-Ward, states that 71 per cent of the hopeless cases of pulmonary tuberculosis at the Manitoba Sanatorium developed symptoms and signs of intestinal tuberculosis; of the far-advanced cases, one-third had definite signs; and of the moderately advanced cases, one-third had suspicious signs of intestinal tuberculosis. Schwatt and Steinbach found tuberculous disease of the intestines with ulceration in 65.3 per cent of 100 consecutive autopsies. Berghoff[2] reports that this condition is present in probably 50 per cent of all cases of far-advanced pulmonary tuberculosis.

On account of the fairly large number of cases of intestinal tuberculosis observed in the U. S. Veterans' Bureau, it was decided to make a study for the purpose of ascertaining the methods of diagnosis, the regimens used in its treatment, and the results of the various forms of treatment. Particular study was made of the effects of heliotherapy, both natural and artificial, on this condition, and an attempt was made to learn if heliotherapy resulted in reparative and healing processes of the tuberculous ulcerations of the alimentary tract, as shown by postmortem findings.

Incidence. The clinical symptomatology and signs of this disease are vague and frequently it is most difficult to recognize the condition because of the fact that pulmonary tuberculosis is accompanied by functional gastrointestinal disturbances which cannot be differentiated from those due to tuberculosis of the intestine. Consequently, if dependence is placed only on clinical symptoms and signs, a large number of cases of intestinal tuberculosis would remain undiagnosed.

Therefore, in consonance with the views of the Trudeau Sanatorium, all patients with pulmonary tuberculosis should undergo a roentgenologic examination for the purpose of ascertaining whether or not tuberculosis of the intestines coëxists.

In reviewing the U. S. Veterans' Bureau postmortem protocols for 1928 it was found that 200 patients had died from pulmonary tuberculosis. Of this number, 121 (60.5 per cent) showed evidence of a coëxisting intestinal tuberculosis, and 79 (39.5 per cent) had no intestinal involvement as seen at autopsy.

Period of Observation. Table I indicates the period of observation of the group of Bureau patients with intestinal tuberculosis. It is noted that the largest number were under hospitalization for various periods less than one year (69.9 per cent).

Age of Patients. M. J. Stewart[3] found that more than one-third of the cases of intestinal tuberculosis, in a series of 1000 autopsies, were among patients under the age of thirty years. This observer also noted that in a series of cases with carcinoma of the intestine 84.5 per cent were over forty years of age; while in a group of cases of hyperplastic intestinal tuberculosis 80.9 per cent were under forty years of age, thus emphasizing the importance of age in differentiating between tuberculosis and carcinoma of the intestine.

The Bureau patients studied constituted a select group, by this it is meant that approximately 90 per cent of all of the exservice men fall within the ages of twenty to forty years, and 10 per cent within

TABLE I.—PERIOD OF OBSERVATION.

Age.	Number of cases.	Per cent.
Less than 3 months	229	27.0
3 to 5 "	177	20.9
6 to 11 "	187	22.0
1 to 2 years	164	19.3
2 to 3 "	56	6.6
3 to 4 "	24	2.8
4 to 5 "	7	0.8
5 to 6 "	5	0.6
Total	849	100.0

the age groups above forty years, so that the findings relative to the age distribution are not of much importance and no definite deductions can be made from the data of Table II.

TABLE II.—AGE OF PATIENTS UNDER TREATMENT FOR INTESTINAL TUBERCULOSIS.

Age.	Number of cases.	Per cent.
21 to 25 years	34	4.0
26 to 30 "	225	26.5
31 to 35 "	360	42.4
36 to 40 "	162	19.1
41 to 45 "	42	5.0
46 to 50 "	17	2.0
51 to 55 "	7	0.8
56 to 60 "	2	0.2

Distribution and Character of Tuberculous Lesions of the Lungs in Intestinal Tuberculosis. The classification of the pulmonic disease according to the schema of the American Sanatorium Association in the group of patients studied showed that 93.95 per cent were far advanced, 4.39 per cent were moderately advanced, and 1.66 per cent were minimal.

Table III indicates the distribution and the character of the tuberculous lesions of the lungs in the group of 841 cases studied.

A review of the data in the table indicates that intestinal tuberculosis is apt to coëxist in cases of pulmonary tuberculosis characterized by exudative or fibroexudative lesions with cavity formation.

Interval of Time Between Diagnosis of Pulmonary Tuberculosis and Detection of Intestinal Complication. Functional gastrointestinal symptoms are prevalent and are commonly seen in pulmonary tuberculosis. These functional digestive symptoms simulate those due to intestinal tuberculosis so that it is frequently impossible to differentiate one set of symptoms from the other. It is particularly difficult to ascertain the exact time when intestinal tuberculosis has

its inception. Erickson,[4] in a study of 100 cases of intestinal disease complicating pulmonary tuberculosis, found that the greatest incidence was from the twelfth to the eighteenth month after the onset of the pulmonary disease.

TABLE III.—DISTRIBUTION AND CHARACTER OF TUBERCULOUS LESIONS OF THE LUNGS IN PATIENTS HAVING INTESTINAL TUBERCULOSIS.

	Exudative.		Fibrotic.		Exudative and fibrotic.		Total.	Per cent.
	With cavitation.	Without cavitation.	With cavitation.	Without cavitation.	With cavitation.	Without cavitation.		
Unilateral	1	6	5	18	14	5	49	5.8
Bilateral with less than one-third of better lung involved	14	6	14	24	55	27	140	16.6
Bilateral with more than one-third of better lung involved	244	24	25	9	321	29	652	77.6
Total cases	259	36	44	51	390	61	841*	100.0
Per cent	30.8	4.3	5.2	6.1	46.4	7.2	..	100.0

* Six cases were reported as having no pulmonary tuberculosis; 2 cases were reported as undetermined.

The data noted in Table IV constitute the opinion of Bureau physicians on the interval of time between the diagnosis of pulmonary tuberculosis and the detection of an intestinal complication.

TABLE IV.—INTERVAL OF TIME BETWEEN THE DIAGNOSIS OF PULMONARY TUBERCULOSIS AND CLINICAL EVIDENCE OF INTESTINAL TUBERCULOSIS.

	Number of cases.	Per cent.
Less than 1 month	40	4.8
1 to 6 months	70	8.3
7 to 12 "	58	6.9
1 to 2 years	141	16.7
2 to 3 "	138	16.4
3 to 4 "	92	10.9
4 to 5 "	66	7.8
5 to 6 "	50	5.9
6 to 7 "	57	6.8
7 to 8 "	50	5.9
8 to 9 "	25	3.0
9 to 10 "	29	3.4
10 to 11 "	6	0.7
11 to 12 "	5	0.6
16 "	1	0.1
Unkown	15	1.8
Total	843*	100.0

* Six cases reported as having no pulmonary tuberculosis.

Duration of Symptoms of Onset of Intestinal Tuberculosis. As was stated, the symptoms of onset of intestinal tuberculosis are as a rule vague, so that in a great many instances it is difficult to definitely recognize the condition. A study was made of the symptoms of onset of the Bureau patients having intestinal tuberculosis and the results may be seen by referring to Table V.

TABLE V.—DURATION OF SYMPTOMS OF ONSET OF INTESTINAL TUBERCULOSIS.

Age.	Number of cases.	Per cent.
Less than 1 month	114	13.4
1 to 6 months	304	35.8
7 to 12 months	129	15.2
1 to 2 years	113	13.3
2 to 3 "	56	6.6
3 to 4 "	34	4.0
4 to 5 "	15	1.8
5 to 6 "	6	0.7
6 to 7 "	13	1.5
7 to 8 "	12	1.4
8 to 9 "	3	0.4
9 to 10 "	7	0.8
Unknown	43	5.1
Total	849	100.0

Symptomatology. In a great many cases there may be a history of previous gastrointestinal symptomatology, such as constipation and indigestion, not related to tuberculosis of the intestine—these being followed by an insidious train of symptoms due to tuberculous disease with the result that a definite diagnosis is not always possible, and, when finally made, the patient is in an advanced stage of the disease.

Stewart[5] maintains that the earlier symptoms are usually referable to small-bowel lesions, the later symptoms to disease of the large bowel. According to this author, nervousness, slight impairment of appetite, and constipation beyond usual, constitute the most common early diagnostic symptoms of intestinal tuberculosis. Archibald found that constipation is a special symptom of ulceration of the small bowel, while diarrhea is an indication of disease of the large bowel. Alternating diarrhea and constipation, he thinks, indicate ulceration in both tracts.

Table VI shows the relative frequency of the various symptoms of intestinal tuberculosis observed in the Bureau cases.

Methods of Diagnosis. Erickson[4] maintains that the frequency of the occurrence of intestinal tuberculosis as a complication of the pulmonary form is quite out of proportion to the frequency of its diagnosis. Stewart[5] holds that intestinal involvement does not necessarily begin with the far-advanced stage of pulmonary tuberculosis. Failure to recognize this complication earlier reflects the

inadequacy of our present diagnostic methods, and the necessity and value of the roentgenologic diagnostic technique as developed by Brown and Sampson.[6]

TABLE VI.—SYMPTOMS OF INTESTINAL TUBERCULOSIS.

	Number of cases.	Per cent.
Tenderness or colicky pain in abdomen	581	68.4
Loss of weight	505	59.5
Gas formation	470	55.4
Impairment of appetite	460	54.2
Discomfort after meals	381	44.9
Diarrhea	334	39.3
Emaciation	329	38.7
Dyspepsia	306	36.0
Alternating constipation and diarrhea	265	31.2
Nausea	261	30.7
Nervousness and irritability	251	29.6
Constipation	231	27.2
Vomiting	207	24.4
Bleeding	49	5.8
Mass formation	34	4.0

Table VII indicates the several diagnostic methods used by the Bureau physicians in detecting intestinal tuberculosis in the group of 849 patients under consideration.

TABLE VII.—DIAGNOSTIC METHOD BY WHICH INTESTINAL TUBERCULOSIS WAS FIRST RECOGNIZED.

	Number of cases.	Per cent.
Roentgen ray, clinical symptoms and physical signs	368	43.3
Clinical symptoms and physical signs	306	36.0
Autopsy	107	12.6
Roentgen ray, alone	65	7.7
Laparotomy	3	0.4
Total	849	100.0

Comparative Value of Various Diagnostic Methods. A study of Table VIII shows that in the examination of 587 patients for tuberculosis of the intestine of the total number under discussion the combined clinical and roentgenologic methods yielded the best results. The disease was definitely diagnosed by these two methods in 389, or 66.27 per cent of the cases.

TABLE VIII.—COMPARATIVE VALUE OF VARIOUS DIAGNOSTIC METHODS.

	Number of cases.	Per cent.
Positive both clinically and by Roentgen ray	389	66.3
Positive clinically and negative by Roentgen ray	96	16.3
Positive by Roentgen ray and negative clinically	51	8.7
Negative both clinically and by Roentgen ray and in which diagnosis was made at autopsy	48	8.2
Positive clinically but negative by Roentgen ray and at autopsy	2	0.3
Positive by Roentgen ray and negative at autopsy	1	0.2
Total	587	100.0

Treatment. In order that treatment may be effective it is essential that an early diagnosis be made and that therapeutic measures be instituted as soon as the condition is recognized. Measures aimed at controlling gastrointestinal symptoms and which result in an improved digestion and assimilation will no doubt benefit the patient and increase his resistance against the progress of both the pulmonary and intestinal tuberculosis.

In the treatment of intestinal tuberculosis rest is most essential; in addition a bland diet, with a minimum amount of roughage, and one which is readily digested and assimilated will help the patient in combating the tuberculous infection.

There are a series of digestive symptoms which are most depressing on the patient and which interfere with his fight against the disease. These require symptomatic medicinal treatment such as calcium chlorid—the latter having been found very helpful, particularly in cases with hyperperistalsis. It seems to act as an antispasmodic when administered intravenously.

When tuberculosis of the bowel is localized and can be eradicated, surgery is the treatment of choice. In resorting to surgery, it is essential that the condition be recognized before it has had an opportunity to spread.

A discussion of the treatment of intestinal tuberculosis would be incomplete without a reference to heliotherapy, both natural and artificial. Many observers have found that heliotherapy is a reliable means of controlling the symptoms of this disease. Erickson[7] states that the proof of the action of ultraviolet light in tuberculosis is empirical, but that it has a decided effect on the vaious forms of tuberculosis, possibly through stimulation of the calcium metabolism with a resulting sedative action on the motor mechanism of the intestinal tract. He holds that on this theoretical basis the results of heliotherapy may be divided into two stages; a primary or palliative one as shown by symptomatic relief, and a secondary or curative stage which is evident in the Roentgen ray pictures considerably later.

TABLE IX.—METHODS OF TREATMENT OF INTESTINAL TUBERCULOSIS.

	Number of cases.	Per cent.
Rest	643	75.7
Dietetic	467	55.0
Medicinal	381	44.9
Heliotherapy (artificial)	312	36.8
Calcium chlorid	62	7.3
Heliotherapy (natural)	55	6.5
Surgical	13	1.5
Oxygen therapy	2	0.2

Table IX lists the various regimens used in the Bureau hospitals in the treatment of intestinal tuberculosis. Some of these were in

combination. It is noted that rest, diet, ultraviolet radiation, natural heliotherapy and medicinal therapy including calcium chlorid were the most common therapeutic measures used.

Results of Treatment. Table X indicates the results following the treatment of 849 Bureau patients with intestinal tuberculosis. The statistics point to the fact that treatment is not as hopeless as was formerly believed and that some cases may improve and may even be cured.

It was interesting to learn that of the patients with intestinal tuberculosis who were cured or improved following hospitalization 45.36 per cent showed improvement, arrest or cure of the pulmonic disease while 54.64 per cent of the cases showed a stationary or a retrogression of the pulmonic disease.

TABLE X.—RESULTS OF TREATMENT OF INTESTINAL TUBERCULOSIS.

	Number of cases.	Per cent.
Cured (complete disappearance of clinical symptoms and Roentgen ray signs)	16	1.9
Improved	180	21.2
Unimproved	226	26.6
Worse	67	7.9
Died	360	42.4
Total	849	100.0

Distribution of Intestinal Lesions. It is not always possible to determine the exact location of the tuberculous lesions, inasmuch as the disease may be present in a number of portions of the small and large intestines.

The data contained in Table XI were obtained by clinical and roentgenologic means and at postmortem, and show the relative frequency of the tuberculous lesions in the different portions of the small and large intestines.

TABLE XI.—DISTRIBUTION OF LESIONS OF INTESTINAL TUBERCULOSIS IN 849 BUREAU PATIENTS.

Location.	Number of cases.	Per cent.
Cecum	444	52.3
Ileum	328	38.6
Ascending colon	271	31.9
Transverse colon	170	20.0
Ileocecal valve	126	14.8
Descending colon	96	11.3
Jejunum	70	8.2
Appendix	64	7.5
Duodenum	50	5.9
Rectum	31	3.7
Sigmoid	21	2.5
Peritoneum	72	8.5
Large portion of intestinal tract	28	3.3

Foci of Infection of Intestinal Tuberculosis. Ulcerative intestinal tuberculosis is almost always secondary to tuberculosis of the lung. The hyperplastic variety is usually a primary infection. In a small percentage of cases foci of infection are found in organs other than the lungs. These findings are shown in Table XII. It is noted that there were 879 foci of infection in 849 cases; that is, there was more than one focus of infection in certain of the cases.

TABLE XII.—FOCI OF INFECTION OF INTESTINAL TUBERCULOSIS.

	Number of cases.	Per cent.
Lungs	828	97.5
Bone	14	1.6
Urogenital tract	7	0.8
Abdominal lymph nodes	4	0.5
Pleura	3	0.3
Thoracic lymph nodes	1	0.1
Joints	1	0.1
Other organs	21	2.5
Total	879	

Complications. The pathology of intestinal tuberculosis is primarily one of tubercle formation. After a coalescence of the tubercles there is a tendency to disintegration and multiple ulcer formation. Tuberculous ulcers very seldom perforate due to the fact that there is a tendency to new tissue formation. The end-results of a tuberculous ulcer may be: Stenosis of the bowel with obstruction, or perforation followed by peritonitis. Table XIII indicates the frequency of these complications in 490 cases of the total number studied.

TABLE XIII.—COMPLICATIONS OF INTESTINAL TUBERCULOSIS SHOWING INCIDENCE OF ULCERATION, PERFORATION OR OBSTRUCTION.

	Number of cases.
Ulceration of intestine	453
Perforation of intestine	17
Obstruction of intestine	20
Total	490

Roentgenologic Characteristics of Intestinal Tuberculosis. Brown and Sampson[6] teach that no moderately or far-advanced case of pulmonary tuberculosis can be assumed to have been thoroughly examined unless a Roentgen ray study of the bowel has been made. This is the only method which will enable one to detect tuberculous involvement of the alimentary tract in its incipiency or which will make it possible to exclude the disease at any stage.

There are a number of roentgenologic signs frequently found in this disease, which may also be present in nontuberculous conditions of the alimentary tract, but when found in a case of pulmonary or

extrapulmonary tuberculosis the probabilities are that the condition is one of intestinal tuberculosis.

Table XIV indicates the relative frequency of the various roentgenologic signs of intestinal tuberculosis encountered in the group of Bureau cases.

TABLE XIV.—ROENTGENOLOGIC CHARACTERISTICS OF INTESTINAL TUBERCULOSIS IN A GROUP OF 849 BUREAU PATIENTS.

	Number of cases.	Per cent.
Filling defects in cecum and ascending colon	312	36.7
Irregularity of outline of cecum and loss of haustral segmentation of ascending colon	251	29.6
Hypermotility at six hours	219	25.8
Hypermotility at twenty-four hours	216	25.4
Filling defects in portions of large intestine other than cecum and ascending colon	145	17.1
Ileal stasis with delay in filling the cecum	112	13.2
Roentgen ray changes noted by enema	37	4.4
Fixation of cecum	27	3.2

The Clinical Laboratory as an Aid in Diagnosis. On account of the vague symptomatology of intestinal tuberculosis it is necessary to employ any diagnostic methods which may assist the clinician in the detection of the disease. The usefulness and importance of the Roentgen ray laboratory in the diagnosis of intestinal tuberculosis has already been commented on. An attempt was also made to ascertain the value of the clinical laboratory in the detection of the disease. Accordingly a study was made of the various laboratory methods used in the examination of a group of 527 Bureau patients. The result of the study may be seen by referring to Table XV.

It would appear that clinical laboratory findings do not offer very much assistance in the detection and early diagnosis of intestinal tuberculosis. Even in those cases in which tubercle bacilli are found in the feces it is probable that the organisms have their origin in the sputum.

TABLE XV.—CLINICAL LABORATORY DIAGNOSIS OF INTESTINAL TUBERCULOSIS.

	Number of cases.
Tubercle bacilli in feces with tubercle bacilli also in sputum	84
Increase of number of monocytes in blood	65
Blood (occult)	56
Blood (gross)	50
Tubercle bacilli in feces with no tubercle bacilli in sputum	8
No clinical laboratory signs	264
Total	527

Cause of Death. Death of cases of intestinal tuberculosis is due to the spread of the intestinal or pulmonic disease or to a complication of some kind, such as peritonitis, perforation, or meningitis.

There were 360 deaths in the series of 849 cases under consideration. The various causes of death may be noted by referring to Table XVI.

TABLE XVI.—CAUSE OF DEATH.

	Number of cases.	Per cent.
Extension of intestinal or pulmonic tuberculous disease	314	87.2
Tuberculous peritonitis	13	3.6
Intestinal obstruction	12	3.3
Intestinal perforation	9	2.5
Tuberculous meningitis	2	0.6
Hemorrhage of intestines	1	0.3
Other causes	9	2.5
Total deaths	360	100.0

Lesions of Intestinal Tuberculosis as Seen at Autopsy. In order to ascertain the effect of various therapeutic measures upon the lesions of intestinal tuberculosis as seen at autopsy, a study was made of the material in a series of 236 postmortem examinations out of a total of 360 Bureau patients dying from intestinal tuberculosis. The results of this study may be noted by referring to Table XVII.

TABLE XVII.—INTESTINAL LESIONS AS SEEN AT AUTOPSY.

	Untreated.	Treated by rest and diet.	Treated by helio-therapy.	Treated by rest, diet and helio-therapy.	Total.
Active ulceration	14	113	12	8	147
Some active ulcers, others healed	1	22	13	3	39
Complete healing of all ulcers	...	...	1	...	1
Regeneration of epithelia	...	9	4	...	13
Flattening of ulcer walls	...	5	3	...	8
Mammillation	...	8	4	...	12
Fibrosis	4	9	2	1	16
Total	19	166	39	12	236

Duration of Treatment by Rest and Diet of Cases Coming to Autopsy. Table XVIII indicates the various periods of treatment of patients with intestinal tuberculosis who died and who came to autopsy. It also indicates the types of lesions found after treatment by rest and diet.

Duration of Treatment by Heliotherapy of Cases Coming to Autopsy. Table XIX indicates the duration of treatment of Bureau patients receiving ultraviolet radiation who died and who came to autopsy.

The data in Table XVIII and XIX would seem to indicate that ultraviolet radiation, either alone or in combination with a rest and diet regimen, does not yield results to prove that it has specific healing action upon tuberculous disease of the intestines. This is

the view held by a number of observers, notably Smithies,[8] who maintains that he is not yet ready to subscribe to the opinion that heliotherapy has any curative influence whatever on the lesions of intestinal tuberculosis. In his experience the study of the pathologic specimens showed such a great variation in the character of bowel lesions and the efforts at resistance that it was difficult for him to prove and to believe that healing actually resulted from heliotherapy. Brown and Sampson[6] hold that inasmuch as a few cases of intestinal tuberculosis recover without any treatment whatever, judgment of the true value of ultraviolet radiation and natural heliotherapy is difficult to make.

TABLE XVIII.—DURATION OF TREATMENT OF CASES COMING TO AUTOPSY WHO HAD BEEN TREATED BY REST AND DIET.

	Active ulceration.	Some active ulcers, others healed.	Regeneration of epithelia.	Flattening of ulcer walls.	Mammillation.	Fibrosis.	Total.
Less than 1 month	35	7	3	..	3	3	51
1 to 3 months	38	9	3	..	2	3	55
4 to 6 "	23	4	2	..	2	2	33
7 to 12 "	11	3	3	1	2	2	22
1 to 2 years	10	3	1	..	1	1	16
Over 5 "	1	..	..	..	..	..	1
Total . . .	118	26	12	1	10	11	178

It is, therefore, reasonable to infer that heliotherapy has a beneficial effect upon tuberculous disease of the intestines, whether or not it may result in a cure of the disease is questionable.

TABLE XIX.—DURATION OF TREATMENT OF CASES COMING TO AUTOPSY WHO HAD BEEN TREATED BY HELIOTHERAPY.

	Active ulceration.	Some active ulcers, others healed.	Complete healing of all ulcers.	Regeneration of epithelia.	Flattening of ulcer walls.	Mammillation.	Fibrosis.	Total.
Less than 1 month	2	..	..	..	..	..	..	2
1 to 3 months	8	2	..	2	2	2	..	16
4 to 6 "	9	..	..	..	..	..	..	9
7 to 12 "	4	5	..	2	2	2	..	15
1 to 2 years	2	5	1	..	..	..	1	9
Total . . .	25	12	1	4	4	4	1	51

Summary and Conclusions. 1. On account of the vague clinical symptoms and signs of intestinal tuberculosis it is difficult to ascer-

tain definitely the exact incidence of the disease as a complication of pulmonary tuberculosis. However, in a series of 200 autopsies of Bureau patients dying from pulmonary tuberculosis, it was found that 60.5 per cent showed evidence of a coëxisting intestinal tuberculosis.

2. Of a series of 849 Bureau beneficiaries hospitalized for intestinal tuberculosis, it was found that the largest number were under observation for various periods up to one year; the next largest number were under observation from one to two years.

3. Of the Bureau patients with intestinal tuberculosis, 93.95 per cent had pulmonary tuberculosis which was classified as far advanced according to the schema of the American Sanatorium Association. Furthermore, 82.4 per cent of the group had tuberculous lesions with cavitation, while 77.6 per cent had bilateral lesions with more than one-third of the better lung involved. The majority of the patients had either exudative lesions or a combination of exudative and fibrotic lesions.

4. The period of time between the diagnosis of pulmonary tuberculosis and the detection of the intestinal complication varied considerably—the largest group showed evidence of intestinal tuberculosis from one to three years after the diagnosis of pulmonary tuberculosis was made.

5. The symptoms of onset of intestinal tuberculosis are vague, so that in many instances it is difficult to diagnose the condition. In the series studied it was found that the largest group gave evidence of intestinal tuberculosis from one to six months before a definite diagnosis was made; the next largest group had symptoms of this condition from seven to twelve months before it was definitely detected. In a number of cases the symptoms of onset existed from one to ten years before a definite diagnosis was made.

6. The most frequent symptoms were: Tenderness or colicky pain in abdomen, loss of weight, gas formation, impairment of appetite, discomfort after meals, diarrhea, emaciation, dyspepsia, alternating constipation and diarrhea, nausea, nervousness and irritability.

7. The diagnosis of intestinal tuberculosis was definitely made in 43.3 per cent by both clinical and Roentgen ray methods; in 36 per cent a diagnosis was made clinically; in 7.7 per cent by a roentgenologic examination; and in 12.6 per cent a diagnosis was not made either clinically or by Roentgen ray but the disease was found at autopsy. In attempting to ascertain the superiority of the various diagnostic methods it was found that the largest number of cases of intestinal tuberculosis was positively diagnosed by both clinical and Roentgen ray means.

8. The most frequent therapeutic regimens used in the Bureau cases in the treatment of intestinal tuberculosis were: Rest, diet,

heliotherapy, both natural and artificial, and medicinal therapy including calcium chlorid.

9. Of the total number of 849 patients with intestinal tuberculosis approximately 21 per cent were improved and approximately 2 per cent were cured, following hospitalization; the rest of the patients were unimproved or were in a condition of retrogression; 42.4 per cent of the patients died. It is thus seen that treatment is not altogether hopeless, as is commonly believed. Some cases may improve and may even be cured following various therapeutic procedures.

10. The most frequent sites of the lesions of alimentary tuberculosis, in the order named, were: Cecum, ileum, ascending colon, transverse colon, ileocecal valve, descending colon, jejunum, appendix, duodenum, rectum and sigmoid. There was involvement of the peritoneum in 8.5 per cent; and 3.3 per cent showed the presence of tuberculous lesions throughout a large portion of the intestinal tract.

11. While the majority of cases of intestinal tuberculosis are almost always secondary to pulmonic disease, in a small percentage of cases foci of infection are found in organs other than the lungs. The most frequent foci of infection of the cases studied were in the: Lungs, bone, urogenital tract, abdominal lymph nodes and pleura.

12. More than half of the cases of intestinal tuberculosis had some complication, such as ulceration, perforation, or obstruction. The most common complication was ulceration of the bowel.

13. The most frequent Roentgen ray signs characteristic of intestinal tuberculosis in the order named, were: Filling defects in cecum and ascending colon, irregularity of outline of cecum and loss of haustral segmentation of ascending colon, hypermotility at six hours, hypermotility at twenty-four hours, filling defects in portions of the large intestine other than in the cecum or ascending colon, ileal stasis with delay in filling the cecum, Roentgen ray changes noted by enema and fixation of cecum.

14. In reviewing the clinical laboratory findings in the group of cases under consideration, it was found that these do not offer very much assistance in the detection and the early diagnosis of intestinal tuberculosis. Even in those cases in which tubercle bacilli are found in the feces it is probable that the organisms have their origin in the sputum.

15. Death of cases of intestinal tuberculosis is due to a spread of the tuberculous infection, or to a complication of some kind, such as peritonitis or meningitis. In the majority of the Bureau cases the cause of death was an extension of the intestinal or the pulmonic disease.

16. Of a series of 236 cases treated by various regimens, who came to autopsy, the majority received routine sanatorium treatment; a small number of the cases received ultraviolet radiation either alone

or in combination with rest and diet. After treatment by the various methods it was found that most of the cases showed the presence of active ulcers at autopsy. A small number showed ulcers which were both active and healed.

A review of the statistical data would lead one to state that ultraviolet radiation, either alone or in combination with rest and a dietetic regimen, had a beneficial effect upon intestinal tuberculosis; but it is questionable whether or not it may lead to a cure.

NOTE.—It is desired to acknowledge the encouragement of the Medical Director of the U. S. Veterans' Bureau in this study, and of the medical officers in the field who were kind enough to furnish the data which form the basis of this paper. It is also desired to acknowledge the assistance rendered by Miss Anne Bambery, Statistical Assistant in the Research Subdivision.

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A CASE OF CONGENITAL HEMOLYTIC JAUNDICE WITH AN UNUSUALLY HIGH PERCENTAGE OF RETICULOCYTES.

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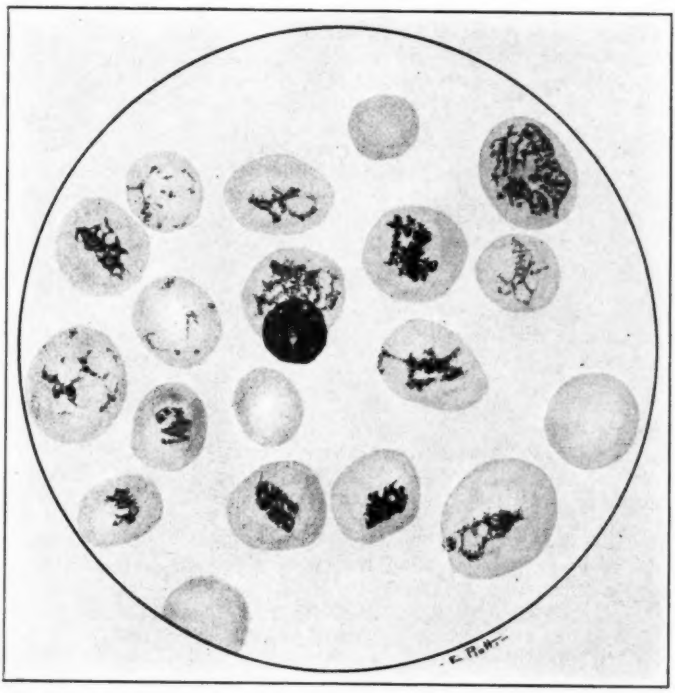
AN increase in the reticulocytes in the peripheral blood as a feature of chronic congenital and acquired hemolytic jaundice was recognized originally by Chauffard in 1907. Meulengracht[1] in his excellent monograph "Der chronische hereditäre hämolytische Icterus" reported reticulocyte counts of 20 to 30 per cent, and many authors (Krumbhaar,[2] Lucas,[3] Piney,[4] Tileston,[5] and others) have given similar figures in each type, the higher percentages tending to occur in the acquired form and during periods of exacerbation of the icterus. Unusually high percentages of immature erythrocytes have not been reported as occurring during the course of either acquired



Drawing from blood smear stained with brilliant cresyl blue and Wright's stain
Reticular material is present in the majority of the cells.

or congenital chronic hemolytic jaundice, although Reynolds[6] obtained counts of 95 per cent in a case of the acquired type in a young adult. Thus we wish to record a case of congenital hemolytic jaundice in which the blood at different times showed extremely high reticulocyte counts.

Case Report. A white male child, aged three years, was referred to this hospital on May 26, 1926, because of jaundice since birth. There was no history of jaundice having occurred in other members of the family. The father, mother and one sibling were living and well. One child had died at the age of eleven months of pneumonia. The patient had had slight jaundice constantly, with exacerbations associated with acute infections. During the two years previous to entry he had been given hospital care in a neighboring city on three occasions because of jaundice and weakness, closely following the onset of an acute upper respiratory infection characterized by coryza, slight cough, irritability and fever. Each time he showed nonobstructive jaundice of a severe degree, slight generalized lymph-node enlargement, an enlarged spleen and secondary anemia. The anemia had been very severe and transfusion of blood had been given on two occasions, followed each time by distinct improvement in the patient's general condition. The jaundice had gradually diminished as the acute infections subsided.

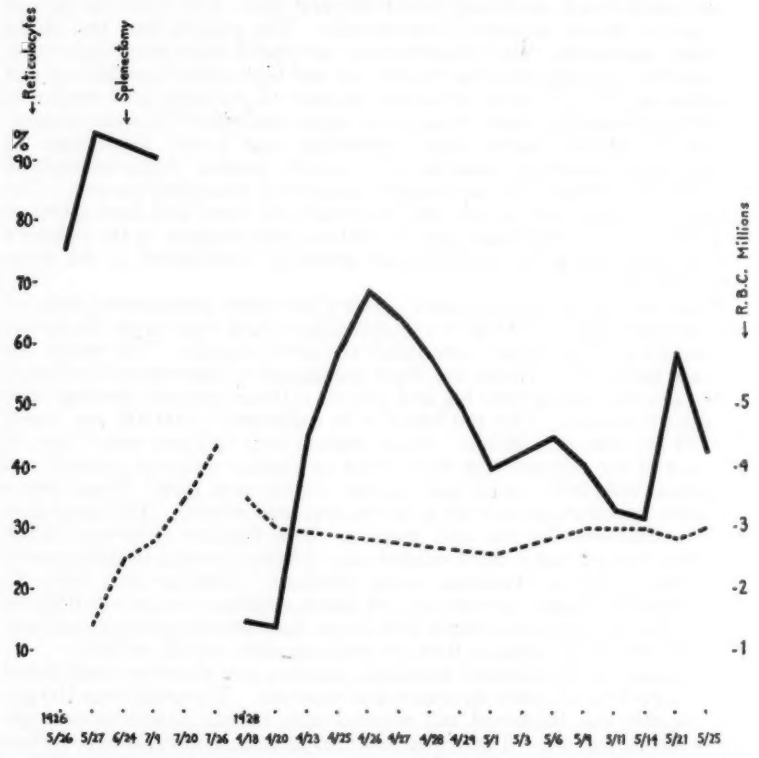
When the patient was first seen in this Clinic there was intense icterus of the skin and scleræ. The liver and spleen were both very large, the former extended 5 and the latter 7 cm. below the costal margin. The spleen was firm and not tender. There was slight generalized enlargement of the lymph nodes and the tonsils were big and cryptic. Other physical findings were essentially normal. The red blood cells numbered 1,200,000 per c.mm. with 30 per cent hemoglobin. When stained with brilliant cresyl blue, 92 per cent of the erythrocytes were found to contain reticular material and occasional cells with nuclei and nuclear bodies were seen. There was a moderate leukocytosis and the platelets appeared normal. The urine gave positive reactions for bile and urobilin. Two fragility tests were interpreted as normal, but a third showed very definite decrease in resistance of the erythrocytes to hypotonic saline solutions. Fragility test, May 27, 1926: hemolysis began in 0.44 per cent saline solution, complete in 0.20 per cent. May 28: hemolysis began in 0.42 per cent, complete in 0.20 per cent. June 10: hemolysis began in 0.68 per cent complete in 0.52 per cent.

The diagnosis of congenital hemolytic jaundice was, therefore, established and two weeks after entry the spleen was removed. The weight was 190 gm. The capsule was thickened and covered with fibrous adhesions over the lower medial surface. The organ was firm in consistency; the cut surface homogeneous and deep red. Microscopic examination revealed a diffuse increase in fibrous tissue in the capsule and trabeculæ and to an even greater degree in the walls of the venules. The sinuses were for the most part empty. There were scattered small groups of myelocytes and nucleated erythrocytes. The corpuscles were numerous; many were large with active germinal centers while others were small and inactive. Diagnosis: splenomegaly with fibrosis and hemopoietic activity.

The patient made an uneventful postoperative recovery with gradual general improvement and was discharged home two months later, a subicteric tint persisting in the skin and scleræ. Following splenectomy, the erythrocytes and hemoglobin rose to 4,500,000 and 70 per cent respectively and the reticulocytes remained about 90 per cent. Two fragility tests on the red blood cells were normal, hemolysis beginning in 0.40 per cent saline solution and complete in 0.30 per cent. The results of these tests, however,

may have been altered by the large number of reticulocytes present since these immature cells are considered to be more resistant to hypotonic saline solutions than the adult forms.

During the next twenty months he seemed much better. However, slight jaundice persisted and mild exacerbations occurred on several occasions following acute upper respiratory infections. He was readmitted to the Hospital in April, 1928, ten days after the onset of such an infection and remained seven weeks. During this time the infected tonsils were removed in an effort to lessen the frequency of the recurring "colds."



Solid line, reticulocytes; broken line, erythrocytes. Showing the peristent elevation of reticulocytes during the two periods of observation.

While in the hospital he showed persistent jaundice of a varying degree. The erythrocytes remained about 3,000,000 per c.mm. and the hemoglobin between 30 and 50 per cent. The leukocyte counts were practically normal with occasional moderate rises. There was a normal to increased number of blood platelets at each examination. The bleeding and clotting times were normal. Fragility tests on the red blood cells were normal. On two occasions, hemolysis began in 0.52 per cent saline solution and was complete in 0.30 per cent, while normal controls showed hemolysis from 0.50 to 0.36 per cent saline. Urobilin was frequently present in the urine in excessive amounts. The reticulocytes at the time of this second admission were 15 per cent. There was a rapid unexplained rise to 70 per cent on

the ninth day in the Hospital and they remained between 30 and 65 per cent until the patient was discharged (chart).

Comment and Summary. The striking feature of this case of congenital hemolytic jaundice is the unusually high percentage of reticulocytes present over a long period of observation. The reports in the literature indicate that the number of immature cells occurring during the course of congenital or acquired hemolytic jaundice rapidly returns to normal following splenectomy. Two years after removal of the spleen the blood of this patient showed reticulocyte counts of 30 to 70 per cent. Although improved, he had not been cured by the operation, and the persistent increase in the percentage of immature red blood cells may be interpreted, together with the persistence of jaundice and anemia and the occurrence of hemolytic crises, as additional indication of continued activity of the disease process.

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A CASE OF ACQUIRED HEMOLYTIC JAUNDICE WITH UNUSUAL FEATURES AND IMPROVED BY SPLENECTOMY.

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The following case is recorded on account of certain unusual features in the clinical picture and laboratory findings, and because of the striking improvement after splenectomy. The patient had an exceedingly large number of reticulocytes in the peripheral blood, only a slight alteration in the fragility of his red blood cells to hypotonic salt solution, and was very deeply jaundiced.

Case Report. E. M. (No. 276495). A single, American, market clerk, aged twenty-one years, was admitted to the Massachusetts General Hospital on May 24, 1926, complaining of weakness and jaundice. He had been well

until seventeen months before admission, when he was seized with a severe cough, accompanied by headache, general malaise, slight chills and a mild degree of fever. He went to bed and at the end of a week he noticed that his skin and scleræ had become yellow and that his urine was of a dark amber and his stools of a dark yellow color. There was no appreciable change in his condition after he had been in bed three weeks, and, although the jaundice and weakness had persisted, he returned to work.

From that time until his admission to the hospital, sixteen months later he was never free from jaundice, but he observed that its intensity varied greatly from time to time. When the icterus was more marked he was dyspneic on slight exertion and too weak to work, while at other periods there was only slight jaundice, and he was able to carry on his regular activities in spite of becoming easily fatigued. Throughout these months he continued to pass dark-colored urine, while his stools always appeared to him normal in color. Two months prior to admission he became more deeply icteric than ever before and so weak that he was forced to return to bed, where he remained until he was brought to the hospital. His appetite had been excellent despite the jaundice, but he lost nearly 25 pounds of weight during his illness.

The patient's past history was entirely negative. He had lived in New Hampshire all his life and had never had any illnesses except measles and mumps. Both of his parents, three brothers and two sisters were living and well, and there was no family history of jaundice, anemia or other familial disease.

Physical Examination. Physical examination showed a well-developed and moderately nourished young man whose skin and scleræ were extremely icteric. The temperature, pulse and respirations were normal. The mucous membranes were extremely pale. The eyes, ears, teeth, nose, throat, lymph nodes, thyroid and lungs presented no abnormalities. The heart was slightly enlarged to the left, and a loud blowing systolic murmur was heard at the mitral area. The abdomen was rather prominent, and the liver was easily palpable 4 cm. below the costal margin, while the spleen could be felt at about the same level in the abdomen. Both of these organs were thought to be smooth, firm and slightly tender on palpation. There was no evidence of fluid in the abdominal cavity, no edema of the extremities and the tendon reflexes were normal.

The Blood. On admission the red blood cell count was 1,500,000 per c.mm. and the hemoglobin was 40 per cent. The red blood cells were characteristic of a marked secondary anemia, with evidence of an extraordinary degree of regeneration. There was a great variation in the size of the cells, with a moderate degree of achromia and a slight variation in shape. Almost every cell was polychromatophilic, some staining much more deeply than others. Two or 3 nucleated red blood cells were seen in each oil immersion field of the microscope. A specimen stained with brilliant cresyl blue showed reticular material in 95 per cent of the red blood cells.

The total white blood cell and differential count were essentially normal, and the blood platelets appeared to be slightly decreased.

In a test of the fragility of the red blood cells there was partial hemolysis in 0.4 per cent aqueous solution of sodium chlorid and complete hemolysis in 0.32 per cent solution, and identical results were obtained in a control of normal blood.

The icteric index of the patient's serum was 100, and a qualitative van den Bergh gave a negative direct and a strongly positive indirect test.

Blood coagulation time, bleeding time, blood Wassermann, blood calcium and phosphorus were normal and there was no autoagglutination of the red blood cells.

Other Examinations. The basal metabolic rate was +25 per cent. Several stools were examined and all were of normal consistency, dark brown in color and showed no evidence of blood either microscopically or by the guaiac test. The urine was dark amber in color at all examinations and acid in reaction. Its specific gravity varied from 1.014 to 1.022. No albumin, sugar or bile was detected by the routine tests, and the sediment was consistently negative. No Bence-Jones protein was found and only a trace of urobilin. The high color was thought to be due to the presence of urates. Gastric analysis and roentgenologic examination of the long bones showed no variation from the normal, and Roentgen rays of the gall bladder region showed no evidence of cholelithiasis.

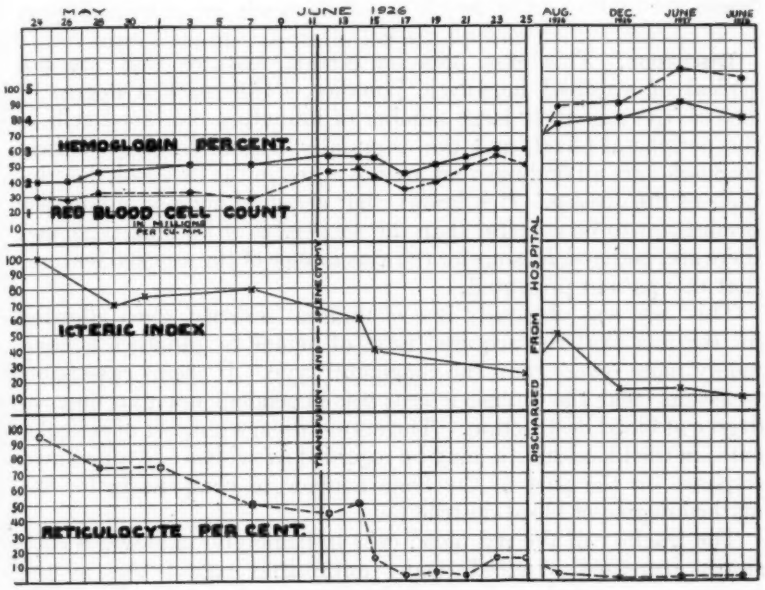

FIG. 1.—Synopsis of Blood studies.

Clinical Course. During the first two weeks of the patient's stay in the hospital the intensity of the icterus was observed to vary considerably from time to time, and there was a corresponding variation in the number of reticulocytes found in the blood stream, but there was otherwise no notable change in his condition. Two and a half weeks after admission he was given a transfusion of 500 cc. of whole blood and splenectomy was performed by Dr. Beth Vincent. At operation the liver appeared essentially normal, although somewhat enlarged and slightly congested. The gall bladder was full and distended, but not acutely inflamed. The spleen was about four times the normal size, soft, dark red in color and its external surface presented two areas of depression, which were thought to indicate old infarctions. There were a few adhesions to the diaphragm, but the spleen was removed without difficulty. The pathologic department made the diagnosis of "splenic hyperplasia." The patient had a normal and brief postoperative convalescence, and was discharged from the hospital two weeks after operation.

The chart on page 551 shows, in graphic form, the striking decrease in icterus and in the reticulocytes, with a corresponding rise in the concentration of the hemoglobin and red blood cells.

The patient returned to work three months after splenectomy and has been at work daily since then. He rapidly regained weight and strength, and, although laboratory tests have continued to show a slight degree of icterus, he has been clinically free of symptoms for three years.*

The fragility of the red blood cells, which was normal at the time of his admission to the hospital, has been tested several times since splenectomy and the results have been variable. At certain examinations their fragility to hypotonic salt solution has been normal and at others slightly increased. At no time have his red blood cells been definitely abnormally fragile.

Discussion. This case presents certain features that are not typical of acquired hemolytic jaundice. The marked degree of icterus, the extremely large number of immature red blood cells in the peripheral blood, and the essentially normal fragility of these corpuscles are all findings that are not noted in the textbook descriptions of the disease. It is known that acquired hemolytic jaundice is more apt to be atypical than the congenital or familial type, and there are, perhaps, reasons for the appearance of the unusual features that this patient presented.

This case was obviously one of unusual severity, even allowing for the fact that the acquired form of hemolytic jaundice is commonly more severe than the congenital type. It seems reasonable to assume that the intense icterus was dependent upon an unusual degree of blood destruction. The extraordinary number of reticulocytes in the blood stream may be regarded as evidence of a maximal response on the part of the bone marrow to compensate for the marked degree of blood destruction.

The fragility of the red blood cells in hemolytic jaundice is classically increased. Indeed, many authorities regard this as the fundamental pathologic basis of the disease. It is, therefore, difficult to account for the essentially normal fragility of this patient's red blood cells. Some investigators believe that immature red blood cells, at least in certain disorders of the blood, are more resistant to hemolysis by hypotonic sodium chlorid solution than are the adult cells, while others hold that this is not the case. New experimental studies concerning this matter are desirable. If, however, the first view is correct, it is conceivable that the large number of reticulocytes found in this case have obscured the fact that the mature red blood cells were abnormally fragile.

* The last blood examination was made on July 16, 1929, and is not recorded in the accompanying chart. At that time the hemoglobin was 85 per cent; the red blood cell count, 5,400,000 per c.mm. The red blood cells were normal in appearance and the total white blood cell and differential counts were normal. A specimen stained with brilliant cresyl blue showed 0.9 per cent reticulocytes. In a test of the fragility of the red blood cells there was partial hemolysis in 0.4 per cent aqueous solution of sodium chlorid and complete hemolysis in 0.25 per cent solution. The icteric index of the serum was 5.

Finally, it is of interest to note that removal of the patient's spleen has apparently resulted in a clinical cure, whereas, in another case of hemolytic jaundice with an unusually high percentage of reticulocytes the same procedure has been of but temporary and far less definite benefit.

Summary. A young man, entering the hospital after seventeen months of continuous jaundice, presented a marked icterus and a considerable degree of secondary anemia with unusually active blood regeneration. A diagnosis of acquired hemolytic jaundice was made and splenectomy was performed with striking improvement in the icterus, the anemia and the patient's general condition. Three years after operation the patient appears to be clinically well.

REVIEWS.

THE ESSENTIALS OF HISTOLOGY. By SIR EDWARD SHARPEY SCHÄFER, F.R.S., Professor of Physiology in the University of Edinburgh. Twelfth edition. Pp. 628; 758 illustrations. Philadelphia: Lea & Febiger, 1929. Price, $5.00.

FROM its first publication, this work has been a standard among the textbooks in its field. The present edition has been completely revised and numerous new illustrations have been added in the form of photographs.

The book has been written for the use of students and like the previous editions, it will be one of the best guides to histology that is anywhere available.

Each chapter of histology has been completely covered, giving the students complete information about the structure of tissues and organs and the development of them. It is sufficiently elementary to be used by students yet complete enough for the use of advanced workers as a key to the interpretation of larger works.

G. R.

THE NORMAL AND PATHOLOGICAL PHYSIOLOGY OF BONE: ITS PROBLEMS. By R. LERICHE and A. POLICARD. Pp. 236; 33 illustrations. St. Louis: The C. V. Mosby Company, 1928. Price, $5.00.

IN a terse but frequently involved manner Leriche and Policard present much data, a few facts, many opinions and a wealth of hypothesis concerning the physiology and pathology of bone. This treatise, while stimulating, leaves one with a feeling of regret that the procedures of their experiments are not given in sufficient detail to permit the reader to draw his own conclusions. It is one thing to speak with authority from incontrovertible proof and another to so speak without the presentation of proof for statements made.

The monograph warrants a careful and unbiased study, as it is controversial; it has been well received and most favorably reviewed. In all likelihood this work will supply the stimulus for intensive investigations by other workers.

The illustrations, while chiefly diagrammatic, are good; the footnote comments of the translators are pertinent. G. W.

THE LAYMAN LOOKS AT DOCTORS. By S. W. and J. T. PIERCE. Pp. 251. New York: Harcourt, Brace & Co. Price, $2.00.

IT is a great pity such a book as this was ever published. It will not hurt the medical profession but I think that it is capable of doing much harm to the reading public. The book is little else than the popularizing of Freudian psychoanalysis, and the description of the lady's difficulties, though very incomplete from a clinical point of view, nevertheless gives one the impression that she is a cyclothymic individual and that she is suffering from a depression with suicidal impulses. That this depression had to run its course and that it was fortunate for pyschoanalysis that she tried it at the end instead of at the beginning of her illness, is of course evident. The description of her experiences at the various sanitaria does not ring true, but reminds one very strongly of the stories that psychotics are inclined to tell of their experiences during an attack, even to the point of giving all the credit for their recovery to the hospital, or the doctor, or the particular form of treatment which they were undergoing when it took place.

As is well known, there is no method of treatment yet discovered that changes the periodicity of manic depressive episodes, or that materially shortens the attacks. The best that any of us has been able to do is to modify these attacks through building up the insight of the patients so as to avoid unnecessary mental and physical strain, and as far as possible insuring the greatest possible physical and mental normality by daily activities. It is only those who have gained insight who do not identify their symptoms and the fact that they do not get well immediately with the treatment they are receiving during the attack; and likewise it is only those who have gained insight who do not credit some coincidental circumstance with their recovery. The patient retails experiences in sanitaria, presumably for mental diseases, run by the old-time custodial type of psychiatrist who is fortunately becoming rare, or in the so-called Nursing Homes run by faddists or general practitioners. If the lady had hysteria she was out of place in either type described; if she had a mental disease, as I believe she had (if her account is genuine), then she was in the right place to begin with, though unfortunately under the least skilled and poorest type of psychiatrist available. Nevertheless, I believe if she had remained in the first hospital that she would have recovered there at approximately the same date that she did under the psychoanalyst.

The book is dangerous and liable to do harm because, as first explained, psychoanalysis should not get the credit. This method may be of some benefit, but only in qualified hands and only when applied to a very restricted type of case. I have had an occasional psychasthenic who was said to have been benefited by this treatment; on the other hand, it has been my sad experience to see many cases

which have been distinctly harmed by it. So, to have a book go forth which recommends, apparently from the unprejudiced point of view of a layman, psychoanalysis as a universal panacea, I believe to be a great pity.

It is unfortunate that the word psychoanalyst has come to mean Freudian analysis; for of course the constructive and synthetic means of reëducation or any other rational treatment of mental disorders must be based upon the analysis of the mental and emotional make-up of each patient, as well as the environmental elements and problems which are in his life. In many cases a profound and exhaustive analysis is not necessary; but in many others the crux of an individual's difficulty is much more subtle, much less easily recognized, perhaps, by him, and then the research must necessarily be a more thorough affair. It is quite true that a rational analysis as a basis of reëducation is not only desirable but necessary. However, tracing a claustrophobia to infantile impressions received during parturition, as is done in this book, is a typical absurdity of the Freudian School and one that a reasonably good neurologist or anyone with the slightest familiarity with embryology could not make. The truth is that the Freudians are for the most part plainly maladapted individuals and thoroughly uncontrolled thinkers. A. R.

THE MEDICAL MUSEUM. BASED ON A NEW SYSTEM OF VISUAL TEACHING. By S. H. DAUKES, O.B.E., M.D., D.P.H., D.T.M. AND H. Pp. 172; 44 illustrations. London: The Wellcome Foundation, Ltd.

THIS book is not merely a theoretical contribution to the improvement of museums in general and medical museums in particular, but a description of practical achievement.

The author is precise, clear and has obviously devoted much study, skill and care to a subject on which this book stamps him as an expert. Having in the first chapter discussed the functions of a medical museum and made a plea for reform and for a wider outlook, Dr. Daukes proceeds in subsequent chapters to describe and discuss the details of the new system of visual teaching on which the ideal medical museum is based.

This is followed by appendices dealing with the application and development of the system, with types of buildings, walls, screens, cases, labels, illustrations and technical details of preserving and mounting specimens. In conclusion there is a valuable and complete bibliography of technical museum publications and 45 whole-page illustrations of screens, sections and specimens which are most helpful as providing practical evidence of the soundness and practicability of this new system of visual teaching. W. F.

THE NUTRITION OF HEALTHY AND SICK INFANTS AND CHILDREN. By E. NOBEL, PROF. C. PIRQUET and P. WAGNER. Translated by BENJAMIN M. GASUL, B.S., M.D. Second revised edition. Pp. 243; 78 illustrations. Philadelphia: F. A. Davis Company, 1929. Price, $3.50.

THIS translation brings the ingenious nutritional system of the recently deceased von Pirquet to the attention of the English speaking physician. Couched in excellent English idiom, clear and brief in explanation, it renders understandable this system so noted for its complicated, symbolic terminology.

The first part of the book considers the theoretical aspects of nutrition, the properties of the food elements and the nutritional requirements of children as computed by the "nem" system.

The second part is devoted to the practical aspects of the same subject, both for normal and for sick children. The diarrheal disorders are very simply classified as acute mild, acute severe, chronic mild and chronic severe. There is a very excellent discussion of the subject of food tolerance and a presentation of its principles by charts. This is a subject highly stressed by the authors, but very briefly dismissed in almost all American books on infant feeding. Nutritional management is outlined in infectious, nervous and metabolic diseases such as nephritis, pertussis, enuresis and diabetes.

Finally, there are about 38 pages of recipes, formulas and diets which the reviewer feels are in themselves sufficient reward for his reading. J. S.

CORONARY THROMBOSIS: ITS VARIOUS CLINICAL FEATURES (MEDICINE MONOGRAPH XVI). By SAMUEL A. LEVINE, M.D. Pp. 178; 85 illustrations. Baltimore: The Williams & Wilkins Company, 1929. Price, $3.00.

IT is only in recent years that it has been possible to separate the coronary thrombosis syndrome during the life of the patient from that of angina pectoris. Though energetically studied and written upon, the subject has not hitherto been comprehensively treated. It is an appropriate service, therefore, for the Medical Monograph Series to fill the gap and the task has been well done by Dr. Levine, himself an important contributor to the field. A conventional form of treatment is followed (General considerations, etiology, symptoms diagnosis, prognosis, treatment and so forth). Pathologic considerations—a term apparently confused with morbid anatomy—are curiously placed between treatment and the large section devoted to case reports. Every up-to-date internist should familiarize himself with the contents of this book. E. K.

GASTRIC AND DUODENAL ULCER. By ARTHUR F. HURST, M.A., M.D. (OXON.), F.R.C.P., and MATTHEW J. STEWART, M.B. (GLASGOW), F.R.C.P. Pp. 544; 159 illustrations. New York: Oxford University Press, American Branch, 1929. Price, $20.00.

THE authors have covered their subject in a most thorough, scientific and painstaking manner. Peptic ulcer is discussed from every standpoint, including anatomy, physiology, symptomatology and pathologic. A great number of statistical tables aid the reader in forming accurate and helpful conclusions, concerning indications for operation, the results of the various types of surgical procedures employed and the ultimate results both in mortality and morbidity. Many excellent illustrations enhance the value of the text. The line drawings of the radiograms are a distinct help to the beginner as well as the more experienced clinician. There is a surprisingly small page space taken up by poor and ill-chosen reproductions of old cuts. The colored plates are very good and captioned helpfully. The reader has here some five hundred pages of reference, statistics and bibliography that are extremely helpful to him as a teacher, diagnostician and surgeon. E. E.

COMMON INFECTIONS OF THE FEMALE URETHRA AND CERVIX. By FRANK KIDD, M.A., M.CH. (CANTAB.), F.R.C.S. (ENG.) and A. MALCOLM SIMPSON, B.A., M.B., D.P.H. (CANTAB.) Second edition. Pp. 197; 14 illustrations. New York: Oxford University Press, American Branch, 1929.

THIS excellent manual of gonorrhea in women was reviewed five years ago upon the appearance of the first edition. The present edition consists in the adding of a chapter on advances in technique, among which may be mentioned urethral dilatation and painting, the use of acriflavin in glycerin, suction, diathermy and amputation of the cervix. Vulvovaginitis in children is now treated by a paste of Bulgarian milk and castor sugar. P. W.

THE NERVOUS SYSTEM. By E. E. HEWER, D.SC. (LOND.), and G. M. SANDES, M.B., B.S. (LOND), M.R.C.S., L.R.C.P. Pp. 104; 55 illustrations. St. Louis: The C. V. Mosby Company, 1929. Price, $6.50.

MEDICAL students will be grateful for this volume. Clarity and brevity rule throughout and this treatment of a very complex subject has been achieved through the inclusion of many aptly chosen diagrams distributed throughout the text. The minute structure

and function of the component parts of the nervous system are given together but gross anatomy has been omitted.

Among other chapters included in Part I, are the neuron theory, changes following section of nerves; connections of the cerebellum, cranial nerves and basal ganglia; spinal fluid and autonomic system. Part II discusses sensory, motor, visual and cochlear pathways; cerebral cortex, reflex action, levels of integration and mechanism of coördinated muscular movement, together with other topics. Generally, pathology is not considered except hemi- and complete section of the cord, aphasia and nystagmus; but entire chapters are given to "results of interference" at many different levels. There is a comprehensive bibliography and a good index. N. Y.

THE NERVOUS CHILD. By HECTOR CHARLES CAMERON, M.A., M.D. (CANTAB.), F.R.C.P. (LOND.). Fourth edition. Pp. 249; 8 illustrations. London: Oxford University Press, American Branch, 1929.

AN endorsement by the Bureau of Education of the Department of the Interior, Washington, D. C., together with the numerous and rapidly appearing editions and reprintings, speak emphatically of the usefulness of this little volume.

Designed primarily for mothers, on the care of preschool children, its actual realm extends well beyond that period, and may with profit be read by physicians, nurses and teachers.

Chapters range all the way from "Toys, Books and Amusements," to "The Underlying Disturbances of Metabolism in the Nervous Child." To really appreciate its merits—its many helpful and unusual suggestions—one must read the book. N. Y.

BOOKS RECEIVED.

NEW BOOKS.

*Chemistry for Nurses.** By IRENE KOECHIG, A.M. Pp. 304; 7 illustrations. Philadelphia: Lea & Febiger, 1930. Price, $2.75.

Research and Medical Progress and Other Addresses. By J. SHELTON HORSLEY, M.D. Pp. 208; 6 illustrations. St. Louis: The C. V. Mosby Company, 1929. Price, $2.00.

The addresses have to do largely with factors that make for medical progress and improvement in medicine, and do not deal with technical details of surgical procedures.

*Die Medizin der Gegenwart in Selbstdarstellungen.** Pp. 219. Leipzig: Felix Meiner, 1929. Price, 8.50 Mk.

* Reviews of titles followed by an asterisk will appear in a later number.

*Disease and the Man.** By GEORGE DRAPER, M.D. Pp. 270; 52 illustrations. New York: The Macmillan Company, 1930. Price, $4.50.

Tuberculosis in Public School Children. By EUGENE L. OPIE, M.D. and collaborators. Pp. 636; 43 illustrations. Reprinted from The American Review, Vol. 20, No. 4, October, 1929.

Surgery at the New York Hospital One Hundred Years Ago. By EUGENE H. POOL and FRANK J. MCGOWAN. Pp. 188; 24 illustrations. New York: Paul B. Hoeber, Inc., 1929.

The Medical Clinics of North America, Vol. 13, No. 4 (Philadelphia Number) January, 1930. Pp. 301; 13 illustrations. Philadelphia: W. B. Saunders Company.

*Bibliotheca Osleriana.** *A Catalogue of Books illustrating The History of Medicine and Science* collected, arranged, and annotated by SIR WILLIAM OSLER, Bt. Pp. 785. Oxford: At the Clarendon Press, 1929.

*Roentgenographic Technique.** By DARMON ARTELLE RHINEHART, A.M., M.D. Pp. 388; 159 illustrations. Philadelphia: Lea & Febiger, 1930. Price, $5.50.

*Nursing in Emergencies.** By JACOB K. BERMAN, A.B., M.D., F.A.C.S. Pp. 160; 109 illustrations. St. Louis: The C. V. Mosby Company, 1929. Price, $2.00.

*A Text-book on Orthopedic Surgery.** By WILLIS C. CAMPBELL, M.D., F.A.C.S. Pp. 705; 507 illustrations. Philadelphia: W. B. Saunders Company, 1930. Price, $8.50.

*Surgery of the Lung and Pleura.** By H. MORRISTON DAVIES, M.A., M.D., M.CH., (CANTAB.) F.R.C.S. (ENG.). Pp. 355; 104 illustrations. London: Oxford University Press, 1930.

*The Diagnosis of Health.** By WILLIAM R. P. EMERSON, A.B., M.D. Pp. 272; 51 illustrations. New York: D. Appleton & Co., 1930. Price, $3.00.

*Treatment in General Practice.** By HARRY BECKMAN, M.D. Pp. 899. Philadelphia: W. B. Saunders Company, 1930. Price, $10.00.

*The Mechanism of the Larynx.** By V. E. NEGUS, M.S. (LOND.), F.R.C.S. (ENG.). Pp. 528; 160 illustrations. St. Louis: The C. V. Mosby Company, 1929. Price, $13.50.

NEW EDITIONS.

Symptoms of Visceral Disease. By FRANCIS MARION POTTENGER, A.M., M.D., LL.D., F.A.C.P. Pp. 426; 87 illustrations and 10 color plates. Fourth edition. St. Louis: The C. V. Mosby Company, 1930. Price, $7.50.

Essentials of Medical Electricity. By ELKIN P. CUMBERBATCH, M.A., B.M. (OXON.), D.M.R.E. (CAMB.), M.R.C.P. Pp. 443; 127 illustrations. Sixth edition. St. Louis: The C. V. Mosby Company, 1929. Price, $4.25.

Getting Well and Staying Well. By JOHN POTTS, M.D. Pp. 221. Second edition. St. Louis: The C. V. Mosby Company, 1930. Price, $2.00.

*Bergey's Manual of Determinative Bacteriology.** By DAVID H. BERGEY. Pp. 589. Third edition. Baltimore: The Williams & Wilkins Company, 1930. Price, $6.00.

*The Dietary of Health and Disease.** By GERTRUDE I. THOMAS. Pp. 276; 3 illustrations. Second edition. Philadelphia: Lea & Febiger, 1930, Price, $2.50.

* Reviews of titles followed by an asterisk will appear in a later number.

PROGRESS

OF

MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF

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AND

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Tuberculosis of Insidious Onset and of Acute Onset: Necessity of Different Diagnostic Criteria.—Tuberculosis still holds the first rank as the cause of death during the most productive period of life, from fifteen to forty-five years of age, writes POTTENGER (*J. Am. Med. Assn.*, 1928, **93**, 1801). For this reason the disease is of extreme importance to the medical man. It is a well-known dictum that the earlier the diagnosis is made the greater is the likelihood of the patient's recovering. For this reason it is of primary importance to recognize the signs of its early appearance. There are two types of onset—the acute and the insidious. The symptom complex of the latter development is familiar to most every one, whereas the more acute and abrupt onset of the disease is not recognized in many cases. The nature of tuberculous infection depends very largely upon the basis of the allergic response of the individual to the tubercle protein. Reviewing this particular phase of chronic tuberculosis, the author states that tuberculosis differs from most of the acute infectious diseases in that there remains after infection viable organisms in the body likely to cause a series of future reinoculations under certain circumstances. There is not produced a lasting immunity for this reason, and the disease develops because of a succession of reinfections with bacilli and bacillary protein. If the number of organisms is limited, the onset would be insidious. If, on the contrary, a large number of bacilli stimulate the immunologic reactions of the patient, there will be marked allergic phenomena. A toxic syndrome, with rapid pulse, increased temperature, malaise, loss of appetite and poor digestion, with cough, spasticity of the muscles of the shoulder girdle, lagging and bacilli in the sputum takes place. As far as the toxic group of symptoms is concerned, the condition cannot be differentiated

from any other acute infection, but the cough and expectoration should direct attention to the lungs. Repeated examinations of the sputum are therefore indicated. Bacilli will often be found in large numbers. This acute onset is very frequently followed by a period of quiescence during which the toxic symptoms may entirely disappear or may reappear again after a period of time. The patient is presumed to have an acute respiratory tract infection. It is to avoid the possibility of making such a mistake that numerous sputum examinations should be made, particularly if the patient gives a history of having had repeated colds.

SURGERY

UNDER THE CHARGE OF

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Bronchogenic Contamination in Embolic Abscess of the Lungs.—ALLEN, ADAMS and HIDINA (*Arch. Surg.*, 1929, **19**, 1262) say that attention was called to the facts that abscess develops much more readily from embolic than from intrabronchial inoculation of the lung and that the lung appears to be in general much more resistant to necrosis and suppuration than are the other tissues. Experimental test was made of the hypothesis. The greater vitality of the lung in pyogenic infections is due mainly to a greater blood supply and the elimination of the pulmonary circulation as by embolism reduces the blood supply and tissue vitality to that common level. It was concluded that the hypothesis is essentially correct. This principle was applied to explain the pathogenesis of certain suppurative diseases of the lungs, viz.: postoperative abscess of the lung, especially following sterile operations; postpneumonic abscess of the lung, especially following sterile operations; postpneumonic abscess of the lung and empyema and relapses in suppurative diseases of the lung in general. Hemorrhagic infarct may have a similar origin.

Fifteen Years Devoted to the Use of Radium in Neoplastic Diseases.—QUIGLEY (*Urol. and Cutan. Rev.*, 1929, **33**, 800) says that radium has established a definite place in modern medicine. Its field of usefulness is constantly increasing, not only by extensions in the fields in which it has been established, but also in new fields, such as the treatment of exophthalmic goiter and tubercular glands. While the bulk of the radium work is with cancer, radium also has a very wide field of usefulness in benign conditions. Local and accessible cancer should be treated by choice with radium. Cases involving considerable bulk should be treated by means of a combination of preoperative radiations with radium, surgical operation and postoperative radiation. Certain clinical facts concerning cancer growing in certain body locations are fundamental, and these facts must be taken into consideration if we are

to use radiation to the best advantage. Judgment in estimating radium dosage is a thing that can be learned only by long experience. The author knows of no way for physicians or students to acquire skill in the use of radium except by working with someone already skilled in its use.

Surgical Aspects of Undulant Fever.—Supsu and Bowers (*Am. J. Surg.*, 1929, **7**, 597) state that undulant fever has rapidly become a most important public health problem. Over 1000 cases have been discovered in this country in the last few years. Undulant fever possesses important surgical aspects, chiefly because of the ease with which it may be confused with appendicitis and cholecystitis in certain cases. In view of the predilection of the organism for the genital tract it bears an etiologic relationship to certain cases of abortion, tubo-ovarian abscess, seminal vesiculitis, prostatitis, epididymitis and orchitis. The joint manifestations of the disease make it a diagnostic problem for the orthopedic surgeon. Contrary to the frequently expressed belief that undulant fever is difficult to recognize clinically, the clinical manifestations of the disease were sufficiently characteristic to enable physicians to make an initial diagnosis of undulant fever in over one-third of the cases reported here. The relationship between the consumption of raw milk from cattle infected with the organism of contagious abortion (Brucella abortus) and the occurrence of undulant fever in human beings has been established.

The Effects of Hypertonic Dextrose Solution Upon Experimental Diffuse Peritonitis.—Bucbinder, Heilman and Foster (*Surg., Gynec. and Obst.*, 1929, **49**, 788) claim that rapidity of absorption in the largest measure governs the prognosis of acute, diffuse peritonitis. Fibrin is the most important factor in controlling the rate of absorption. Fibrin is diminished or absent in the more virulent cases because of dilution of the exudate. The streptococcus is most commonly identified with this abundant exudate and the accompanying virulent course of the disease. The addition to such an inflammatory exudate of a transudate produced by the intraperitoneal injection of hypertonic dextrose solution produces a more rapid spread of the infection and insures lethal outcome. It seems probable that an abundance of thin exudate serves to prevent ileus by mechanical isolation of intestinal loops. The results of this experimental study do not agree with the published reports of the similar treatment of peritonitis in man.

Tuberculosis of Colon Simulating Cancer.—Bargen, Copeland and Rankin (*Ann. Surg.*, 1930, **91**, 79) say that tuberculous lesions of the colon, as a primary disease, have been reported. When they occur their common site is the ileocecal region. Tuberculosis of the sigmoid colon is one of the rare forms of tuberculosis of the colon. The absence or scantiness of the bleeding in the presence of a large obstructive lesion argues against the presence of malignant conditions. Rankin and Yeomans previously have noted the similarity of the roentgenographic defects produced by tuberculous and malignant lesions. The absence

of tuberculous lesions elsewhere than in the sigmoid colon is noteworthy. Pincoffs and Boggs noted that in tuberculosis of intraäbdominal origin, masses of tuberculous nodules will occur in various places and that there is more matting of viscera than with tuberculosis of distant origin. The absence of lesions in the rectum and in the rectosigmoid portion of the colon, as noted by proctoscopic examination, argues against the presence of an ulcerative type of lesion and further, the absence of deformity or of any defect of the colon elsewhere is evidence against the presence of tuberculosis of the proximal portion of the colon and in favor of the disease being of the hyperplastic type.

Evaluation of Cardiac and Circulatory Stimulants for Surgical Patients.—PHELPS (*Ann. Surg.*, 1930, **91**, 24) states that epinephrin increases the cardiac output for a brief period (less than seven minutes) with a tendency in many instances to return to a point below the original output. Caffein actually diminishes the cardiac output. Camphor-in-oil depresses the cardiac musculature and dilates the coronary vessels. Ephedrin stimulates the accelerator mechanism—large doses depress the heart muscle and cause a fall in blood pressure. Pituitrin constricts the vessels in general, but dilates the heart to a very high degree, immediately after its administration. Strychnin has no tonic effect on the heart. The use of insulin in shock is harmful. Digitalis, in adequate dosage, is a cardiac tonic and a general vasoconstrictor, the action of which is dependable, pronounced and sustained.

The Serology of Syphilis.—KAHN (*Urol. and Cutan. Rev.*, 1930, **341**, 1) noted that five requirements for optimum precipitation are observed in syphilis; optimum concentration of antigenic lipoids in the antigen, proper physical state of antigen suspension, correct quantitative relation between serum and antigen suspension, shaking—as a probable aid in hastening collision between the interacting particles while total dilution of a suspension-serum mixture should be a minimum. The Sach school believes that serum reactions in syphilis fall under immunity reactions. The Landsteiner school believes that there is not sufficient experimental evidence for this view. This brings us to the practical application of serum reactions in syphilis. A positive reaction in a case for diagnosis is generally accepted to mean active syphilis and to indicate therapy. The significance of a positive reaction after intensive therapy, however, is still a matter of opinion among different workers. Some, especially Wile, have for a long time contended that a positive serologic reaction may be an expression of immunity in syphilis to the same degree that a positive Widal reaction may be an expression of immunity in typhoid. Thus there is difference of opinion today as to the significance of positive serologic reaction in relation to syphilis therapy. Further experimental evidence is necessary before the immunological character of these reactions will be fully established. In addition, it is hoped that the laboratory will develop some biologic criteria for cure in syphilis.

THERAPEUTICS

UNDER THE CHARGE OF

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AND

SOMA WEISS, M.D.,

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The Use of Levulose With and Without Insulin in the Control of Severe Diabetic Acidosis.—On the basis of carefully controlled investigations, PUCSKO (*München. med. Wchnschr.*, 1929, **76**, 1755) recommends the intravenous injection of levulose in doses up to 10 gm. in 50 per cent solution combined with the administration of 20 units of insulin intravenously or from 20 to 40 units subcutaneously, for the effective control of ketosis in refractory cases of severe diabetes. In contrast to the very rapid effects of a similar combination of dextrose intravenously and insulin, the levulose insulin combination acts rather slowly, but its action seems to increase with repeated administrations. For immediate control, therefore, an initial administration of the glucose-insulin combination may be advisable, but thereafter the combination with levulose proves effective. After the control of ketosis has been well established, the oral administration of levulose combined with injection of insulin in the customary doses maintains control in a most satisfactory manner and has the advantage over glucose that the treatment can be carried out satisfactorily on ambulatory patients.

The Treatment of Influenza with Para-benzoyl-para-amino-benzoyl-amino naphthol 3 to 6 sodium sulphonate (S.U.P., 36).—During the influenza epidemic of the present year every alternate case in which the disease had not existed over forty-eight hours was treated by PEARCE (*Brit. Med. J.*, 1929, 663) with intramuscularly administered S.U.P., 36. The initial dose was 0.5 c.cm. (representing 0.005 gm.) as a rule, occasionally 0.75 c.cm. If the patient did not recover, a second dose of 0.75 cc. was given on the fourth day following the initial dose. Half the injected patients also received 2 to 5 grains of calomel. A comparison of the average duration of pyrexia, headache, muscular pain, the number of days in bed and the number of days loss of work was distinctly in the favor of the patients treated with S.U.P. 36. The earlier the injection, the greater the benefit derived, according to the author's claim.

Sanocrysin Treatment of Pulmonary Tuberculosis.—According to CLARKE (*Brit. Med. J.*, 1929, p. 576) it is safe to start the sanocrysin treatment of pulmonary tuberculosis with a dose of 0.25 gm. This amount is gradually increased at weekly intervals to 0.75 gm. or to

1 gm. in heavier patients. These larger doses are repeated four or five times at ten-day or fortnightly intervals. Some patients do not tolerate even small doses, and the treatment has to be abandoned. Diarrhea, vomiting, dermatitis, stomatitis, neuritis, albuminuria, febrile reactions and loss of weight are the complications observed. Cachexia, intestinal tuberculosis and disease of the kidneys are contraindications. The most beneficial response was observed in the fibroid type of phthisis—55 per cent of the patients were discharged without tubercle bacilli. In the exudative type of phthisis, with the exception of the early cases, sanocrysin is less beneficial. The beneficial effect manifests itself in the disappearance of the tubercle bacilli from the sputum. The heavy cottony shadows of the Roentgen ray picture may be replaced by well-defined markings. Contraction of the lung may also develop. The moist crepitation may clear up, being replaced by diminished breath sounds. If the disease is entirely unilateral, collapse therapy is preferable and sanocrysin should not be applied. If, in addition to the widespread involvement of one side, there is some involvement of the better lung, combined sanocrysin and collapse therapy is indicated. Sanocrysin is not a cure for tuberculosis of the lungs, but it is a valuable aid to treatment if used with caution and discrimination.

Experimental Studies on Analgesics.—Directing attention to the unsatisfactory basis of our present evaluation of analgesic drugs (HAFFNER (*Deutsch. med. Wchnschr.*, 1929, **18**, 731), discusses a method of accurately determining the analgetic dose of a variety of drugs on mice or rats. Employing this method he finds that the following substances are without analgetic action after systemic administration of the largest possible doses: thebain, apomorphin, scopolamin, coniin, veratrin, aconitin, emetin, yohimbin, camphor, cardizaol and coramin. No definite analgetic action is produced by caffein, quinin, salicylic acid, aspirin, antipirin, tropacocain, sodium bromide and a few others. Mescalin, cocain and many of its substitutes produce a mild analgesia. Those agents which are effective analgesics comprise opium and its preparations, morphin, codein, dionin, papaverin, narcotin, heroin and analogous derivatives of codein or morphin; as well as atophanyl, phenacetin and particularly pyramidon. Comparative studies show that heroin is the most potent preparation for producing analgesia, being twice as active as morphin and only slightly less active than the new preparations, dilaudid and eucodal. Codein has one-third the activity of pantopon or of opium and the relationship between the activity of codein and pyramidon is approximately 1 to 3. Combinations of these several preparations in general show no synergism but merely demonstrate additive effects. On the other hand pyramidon combined with codein or other of the analgetic opium alkaloids produces marked potentiation. Thus one-eighth of the analgetic dose of codein plus one-half the corresponding dose of pyramidon produces complete analgesia. The same effect is obtained from one-third dose of codein plus one-fourth that of pyramidon. This combination, with or without the addition of narcotin, gives analgesia essentially equivalent to that produced by morphin, and is free from the undesirable effects of the latter alkaloid. An effective combination for man is a mixture of 25 mg. each of codein and narcotin with 200 mg. of pyramidon. It is

interesting to note that the various anesthetic and hypnotic preparations, including ether, chloroform, the alcohols and the derivatives of diethylbarbituric acid, and so forth, as well as magnesium sulphate, are virtually without analgesic action except in quantities which produce marked narcosis.

Exceptional Injuries to the Circulation by Insulin.—After reviewing many reported instances of circulatory disturbance caused by insulin, REINWEIN (*Deutsch. med. Wchnschr.*, 1929, **55**, 951), reports in detail on two patients in whom the administration of insulin precipitated extreme degrees of congestive heart failure with all of its associated symptoms, including intense dyspnea, orthopnea and the development of general anasarca. In both the dyspnea was mistaken for the premonitory signs of diabetic coma and increasing doses of insulin were administered with the result that the cardiac failure was further aggravated. Both patients were relieved by the complete withdrawal of insulin, the introduction of virtual starvation, the restriction of fluid intake and the administration of strophanthin, digitalis and other circulatory stimulants. In one the diabetes was subsequently found to be very mild and controllable by diet alone. In the other it was marked and, after restoration of cardiac efficiency, small doses of insulin were necessary. So long, however, as the dose was kept small, no further difficulty with the circulation was encountered. The author points out that the experiences in these two patients further establish the necessity of proceeding cautiously with the administration of insulin in diabetic patients who manifest evidences of organic disease of the heart or circulation.

PEDIATRICS

UNDER THE CHARGE OF

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Vaccination of Children Against Typhoid and Paratyphoid.—HESSE (*Arch. de med. des enf.*, 1929, **32**, 729) points out that nowadays the occurrence of typhoid and paratyphoid is limited principally to women and children. He attempts to explain this by the fact that in military service vaccination against these diseases is compulsory. From a review of the literature and his personal experience he feels that it is absolutely necessary to vaccinate by subcutaneous innoculation all children older than three years of age who live in an environment where the danger of contagion is great. Antidiphtheritic vaccination may be performed at the same time. With the typhoid and paratyphoid vaccination, protection is afforded for a period of only two years, after which revaccination may be done by subcutaneous injection or by taking the vaccine of Lumiere or Besredka. The contraindica-

tions to this procedure are tuberculosis or a weakened general condition and it should not be done in children with an acute infectious disease or in those having symptoms of cardiac or renal insufficiency or liver disorders.

The Pineal Form of Pubertas Precox.—BERBLINGER (*Deutsch. med. Wchnschr.*, 1929, **55**, 1956) describes several forms of precocious puberty. The first type in which either hyperplasia of the suprarenal cortex or hypernephroma is found is more frequent in girls. The second is the genital form which is found in both sexes. In this type there exists other tumors or hypertrophy of the generative glands. The third type is the pineal form. Nearly all the cases so far reported were in boys. It was found that the pathologic changes occurring in this form of precocious puberty differ widely. Some cases were observed in which the pineal body itself was not affected but in which a tumor was found in the third ventricle. It is assumed that the pineal body and the nerve centers in this region are closely interrelated, but he also assumes that there are probably two forms of cerebral precocious puberty which he groups as the pineal type and the diencephalic type. The author further points out that in adult men with glioma of the pineal body hypertrophy of the testes has been observed. From this it would seem that the pineal body exerts an influence on the sex organs even after the age of puberty.

Chest Roentgenograms of Nontuberculous Children Suspected of Having Tuberculosis.—WOLFF and STONE (*J. Am. Med. Assn.*, 1930, **94**, 458) found that the average number of previous diseases per case varied only from 2.2 to 2.6 for the various groups, with the whole series at 2.3. The average number of symptoms presented by each group varied between 1.4 and 1.8 per case. The average age of the whole series was eight years, the youngest patient being two years of age and the eldest fifteen years. It is of special interest that the group without increased markings in the upper lobes are a higher incidence of past respiratory diseases, especially bronchitis, measles and pneumonia, than in the group with increased markings. In one group with an incidence of previous diseases of 1.7 per child, with an average age of 3.5 years, showed in comparison with the clinic group a higher percentage of multiple axial vessels at the hili, a slightly higher percentage of multiple axial vessels up to 2 mm. in diameter in the upper left part of the chest, in vessels of 3 mm. in either lung field and a somewhat lower percentage of localized increase in the lung markings. There was no increase in the number showing positive d'Espine's sign, vertebral dullness, paravertebral dullness and dullness of the manubrium in the cases presenting multiple axial vessels at the hili. The definite impression gained by a survey of the entire study is that there are no marked variations in any of the groups. In roentgenograms of the chest in the children without acute illness and with negative tuberculin reactions may show single or multiple, large or small axial vessels in the hili, multiple axial vessels up to 2 or 3 mm. in diameter in the lung tissue, localized increased lung markings, localized plural thickenings or none of these shadows. From this it is apparent that a diagnosis of tuberculosis of the mediastinal glands or of lung tissue cannot be based on the findings of the

roentgenograms. In this study no calcifications, glandular tumors or localized pulmonary infiltrations were found and no definite correlation was found to exist between positive roentgenogram findings and the clinical history.

The Effect of Large Amounts of Milk Sugar on the Stools and Nutrition of Infants.—BARENBERG and ABRAMSON (*Arch. Pediat.*, 1930, **47**, 1) made a study over a period of more than a year, including both summer and winter months, in order to determine the effects of large quantities of milk sugar on the frequency and the character of the stools of infants. They desire to determine whether milk sugar acted as an intestinal irritant and whether it had a laxative effect in infants when fed even in very high concentrations. The first part of their investigation which was conducted during the summer months showed that ingestion of even 12 to 15 per cent by weight of milk sugar did not bring about loose stools. The second part of the investigation was conducted from January to June. Comparison made with a control group of infants showed that the diarrhea which followed in some was due primarily to the milk sugar, but was secondary to a nutritional disturbance in which infection played the chief part. Sugar was not found in the urine or in the stools either in conditions of health or of disease in spite of the fact that the babies received approximately 15 to 17 gm. of milk sugar per kilogram of body weight. Repeated microscopic examinations of the stools showed that a Gram-negative type of flora predominated at all times and that few Gram-positive, acidophilic organisms were noted. The infants receiving large amounts of milk sugar responded with a better rate of growth than did the control group. Milk sugar is a safe carbohydrate for the modification of cows' milk and does not have a laxative effect in infants when used even in high concentration.

The Relative Digestibility of Unsweetened Evaporated Milk, Boiled Milk and Raw Milk by Trypsin in Vitro.—WALLEN-LAWRENCE and KOCH (*Am. J. Dis. Child.*, 1930, **39**, 18) observed that raw milk when pasteurized, boiled or evaporated undergoes changes which make it more readily digested by trypsin *in vitro* than raw milk. The changes are proportionally greater in boiled and evaporated milk than in pasteurized milk. The increase in trypsin digestibility appeared to be a function of a temperature to which the milk is heated and the length of time for which it is heated. The increase in trypsin digestibility is not correlated with the changes in the buffer system of milk incidental to heating nor is it correlated with any changes in the casein of the milk. The change in trypsin digestibility is due to some heat-labile constituent of the whey. It is thought that this inhibitory substance will be found in the albumin portion of the whey and calcium and phosphate are probably not involved. It has been assumed that the tryptic inhibitant reacts with trypsin to inactivate it, and on this assumption therapeutical curves have been calculated which show a marked resemblance to the curves obtained by actual experiment. The authors feel that no practical significance can be attached to these results until the effect of pepsin digestion as a precursor to tryptic digestion has been studied.

DERMATOLOGY AND SYPHILIS

UNDER THE CHARGE OF

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Industrial Dermatoses: Their Causation, Recognition, Prevention, Treatment.—SIBYL OVERTON (*Brit. J. Derm. and Syph.*, 1929, **41**, 255) stresses the recent prominence of skin affections among industrial disabilities in England. In 1927 more certificates of disability were issued for dermatoses than for any other compensatable condition. Important among the causes of serious cutaneous disabilities are chrome, pitch, tar and alkalies. The latter have held first place as causative factors for the past three years. Other important causes have been degreasing agents such as turpentine and petrol; sugar and dough are also responsible for an increasing number of cases. Important secondary factors are: (1) Minute particles of filings in machine shops mixed with oil and causing microscopic injuries; (2) infection; (3) absence of cleanliness of person and clothing in the sebaceously active male adolescent. Second attacks of dermatitis are common, while factors of sensitization develop as in ordinary cases of dermatitis. An inquiry into certain dyeing and polishing industries has determined that the methods of removal of dyes and chemicals from the hands have been the inciting cause of the ensuing dermatitis. Prevention is necessarily linked closely with causation. "Remove the Cause" does not sum up all preventive measures for dermal irritants must be handled. The problem is to handle them with safety. The author stresses three main preventive procedures: (1) Emollients before and after work, providing both protection and a means of later easy removal of the irritant; (2) complete removal of the irritants by harmless methods several times each working period; (3) frequent inspection by experienced observers to enforce early treatment of minor injuries and burns, scrupulous cleanliness of hands and overalls and removal from irritants with prompt treatment for early cases. Under the same title, DYSON (*ibid.*, p. 264) emphasizes certain common characteristics in the recognition of industrial dermatoses, that is, the occurrence of the inflammation first at the exposed site and the occurrence of a refractory period of sensitization after the subsidence of the acute inflammation recognized by a vasomotor disturbance and significant of the possibility of an early relapse. A liability to relapse reflects a general sensitization comparable to an "anaphylactic state." The general sensitization from prolonged or repeated attacks causes the patient to react to the external irritant on any portion of the skin. Seborrhea and secondary pyogenic infections

appear to favor the appearance of the sensitization phenomena. Predisposition to a trade dermatitis is similar to those of ordinary eczema, that is, hyperidrosis and ichthyosis. The author found a high blood sugar present in cases with intense pruritus, but an inflammatory or discharging surface was accompanied by a slight decrease in blood sugar. Treatment of sensitization cases was effected by the intramuscular injection of the patients' whole blood. The prognosis depends on the duration and the number of previous attacks. With a local or general sensitization the prognosis is less favorable and a relapse becomes almost certain. Treatment in the main means protection from irritants, including soap and water, protection from weather and sudden changes in temperature. Lotions seem to work best in the hyperidrotic patient, while an ointment is indicated for the ichthyotic. Roentgen ray and silver nitrate have proved additional aids in the sensitization cases. Preventive measures should include: (1) Examination before engagement of the employee; (2) periodic medical examinations during employment; (3) the avoidance of the indiscriminate use of emollients as a prophylactic measure, inasmuch as the hyperidrotic workman will be unnecessarily harmed.

GYNECOLOGY AND OBSTETRICS

UNDER THE CHARGE OF

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Prognostic Value of Histologic Findings in Cervical Cancer.—Much work has been done in recent years in an effort to correlate the histologic findings in cases of cervical cancer with the prognosis, and in most instances the investigators seem to be of the opinion that the microscopic picture is of great value. In other words, when the removed specimen shows a histologic picture representative of a high degree of malignancy, the prognosis is relatively poor and *vice versa*. A dissenting opinion has been presented by THIBAUDEAU and BURKE (*J. Cancer Research*, 1929, **13**, 260), which is based upon the results obtained by radiation therapy in cancer of the cervix. In their work they used the classification of Broders, namely: Group 1: Tumors in which 75 to 50 per cent of the cells show differentiation with 25 to 50 per cent of undifferentiated cells. Group 2: Tumors in which 50 to 25 per cent of the cells show differentiation with 50 to 75 per cent of undifferentiated cells. Group 3: Tumors in which 25 per cent or less of the cells show differentiation with 75 to 100 per cent of undifferentiated cells. In their series they found that the histologic grouping and

malignancy indices are of limited value in the prognosis in cases of epithelioma of the cervix. As evidence of this they state that in a series of 28 cases of epithelioma of the cervix in which no recurrence was noted for five or more years following irradiation 25 per cent of the cases belonged to Group 3, 50 per cent to Group 2 and 25 per cent to Group 1.

Vaginal Administration of Follicular Hormone.—In a preliminary note on their experimental work POWERS, VARLEY and MORRELL (*Endocrinology*, 1929, **13** 395) state that they prepared the estrus-inducing hormone of the ovary in the form of a gelatin pessary for vaginal administration. The check of the gelatin pessaries by injection of a watery emulsion of them into white rats showed that no loss in potency occurred in their preparation. They have been able to induce the estrus cycle in spayed albino rats by the vaginal administration of the hormone. The ratio between the pessary dose and the subcutaneous dose is probably about 3 to 1. Menstruation has been induced in spayed monkeys by the vaginal administration of these pessaries, using as low as 150 units. This work would seem to show that satisfactory absorption occurs from the vagina so that this method of administration may be used as a more pleasant manner of administration than the usual and sometimes painful method of subcutaneous injection.

Irradiation of Cancer of the Cervix.—A review of the literature reveals a regrettable diversity of opinion on the radiologic management of cancer of the uterine cervix states LAWRENCE (*Radiology*, 1929, **12**, 429) as he pleads for a standardization in the methods of treatment. He believes that it can be theoretically demonstrated and upheld by recorded results that the gamma rays of radium and Roentgen rays are equally important in the radiotherapeutic management of carcinoma of the cervix and that no one is justified in using one to the exclusion of the other. In early cases radium is of chief importance, but all of these cases would be safer if external radiation were added shortly after radium treatment. In borderline cases radium and Roentgen ray are of equal importance. Either may precede, but the other should follow within a week or ten days as a supplement. In advanced cases the Roentgen ray is of far greater importance than radium and should always be given first. Its action, however, should be supplemented by guarded doses of radium from within as there are no contraindications to such supplementary treatment. Although individual variations in technique are to be expected, the author believes that the profession should be able to agree upon the principles underlying the management of each of the three degrees of this disease.

Nasal Administration of Sexual Hormones.—PRATT and SMALTZER (*Endocrinology*, 1929, **13**, 320), of the Henry Ford Hospital, are quite enthusiastic about the nasal-spray method of administering hormones of the ovary and pituitary gland, since by this method the patient controls the administration and is not obliged to visit the doctor for hypodermic injections. They found that when the hormone has been sprayed into the nose, all of the material appears to be absorbed and there has been no sign nor symptom of local irritation. The method

of administration is so simple that the patients have no difficulty in managing it at home. While there has been no complaint following the use of the plain hormone, some patients prefer a specially scented preparation. When coryza or other local abnormality contraindicates the application to the nasal mucosa, the vaginal mucosa may be used. Frequently repeated doses can be administered by the patient approximating normal conditions in a way that cannot easily be accomplished by hypodermic injections, so that this method increases the field of usefulness of the hormones. They have applied the method to the use of ovarian hormone, pituitrin, pitresin and pitocin and find that it is efficient, easy and safe.

OPHTHALMOLOGY

UNDER THE CHARGE OF

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Pronounced Short-sightedness and the Interruption of Pregnancy.—BIRCH-HIRSCHFELD (*Ztschr. f. Augenh.*, 1929, **68**, 127) reports 3 cases in which myopic women suffered reduction in visual acuity and increasing short-sightedness during pregnancy. In all 3 cases the following pregnancy was interrupted since another, similar advance in the trouble would leave the patients blind or nearly so. While all myopic women do not suffer such a change, he concludes that high-grade myopia of both eyes with advanced central changes in the retina and choroid and pronounced poor sight in one eye with similar, though less marked changes in the other eye justify therapeutic abortion. Particularly is there danger of blindness or poor vision approximating it, due to hemorrhage and vascular obliteration in the better eye if there was a decrease of visual acuity with or without advance in the myopia during the earlier pregnancy.

The Possibility of Influencing Glaucoma by Roentgen Irradiation of the Thyroid.—The significance of increased tonus of the sympathetic in glaucomatous eyes has been suspected by earlier authors. Krasso (*Ztschr. f. Augenh.*, 1929, **68**, 163) investigated 31 patients to determine the relations of basal metabolism and thyroid hyperfunction respectively, and sympathetic tonus in the vascular region of the eye to glaucoma. Five of these were treated with Roentgen rays to determine whether in certain cases a latent hyperthyroidism might be in causal relation to the increase in ocular pressure or whether it had a parallel course, since Roentgen ray treatment of the thyroid can reduce the basal metabolism and make symptoms of hyperthyroidism disappear. In all 5 there was a decrease of the general troubles belonging to the symptom complex of latent hyperthyreosis. In only 2 cases was there a long continued decrease in the ocular pressure together with change in the visual fields and in central vision. In both of these the only

symptoms indicating glaucoma were the appearance of glaucomatous excavation and increase in pressure up to 30 mm. Hg as well as decrease in visual acuity and change in the visual fields. In the 3 other cases the pressure was above 30 mm. Hg and there were also attacks of clouded vision. It would appear that it is possible to find cases of chronic glaucoma in which there is a connection between hyperfunction of the thyroid and vasomotor disturbances on the one hand and glaucoma on the other. The fact that glaucoma is a disease of advanced age while disturbances of the vasomotors and hyperfunction of the thyroid appears in all ages, favors the assumption that here the predominance of the thyroid is due to underfunction of the sexual glands. Borak has found that this hyperfunction of the thyroid during the climacteric is very favorably influenced by Roentgen irradiation. It is impossible to say as yet just what cases of glaucoma will respond to Roentgen irradiation of the thyroid. Basal metabolism is not a determining factor. Neither can the permanence of the change be discussed since the cases here reported have been observed for only five months.

OTO-RHINO-LARYNGOLOGY

UNDER THE CHARGE OF

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Acute Infectious Mononucleosis from the Point of View of an Otolaryngologist.—Although comparatively rare, acute infectious mononucleosis, since first described by Spruant and Evans as a clinical entity, has held forth much in the way of academic and practical interest to the otolaryngologist. As its name indicates one of the outstanding features is a marked increase in the mononuclear cells of the blood; the other preponderating finding consists of enlarged cervical lymph nodes. This characteristic has led to the analogy between "glandular fever" and acute infectious mononucleosis, although there is no proof that they are identical. In describing three cases as acute infectious mononucleosis, LA MOTTE (*Arch. Otolaryngol.*, 1929, **10**, 171) calls attention to the wide latitude in appearance of the pharynges of these patients, varying from virtually normal looking throats to acutely inflamed tonsils or postpharyngeal lymphoid nodules, or even to exudative and ulcerative lesions of tonsils, tonsil stumps, or pharyngeal wall. The causative agent is unknown. The prognosis is good. The lymph nodes rarely, if ever, suppurate. In concluding, the author suggests that "it may be that through the otolaryngologist more cases will be recognized and a deeper study will be made than in the cases here reported, thus contributing, perhaps, to the sum total, of knowledge of this interesting disease."

Trigeminal Disturbances of Otitic Origin.—Long have otolaryngologists been concerned about the transmission of impulses of pain to the ear from the sphenopalatine region and other parts of the trigeminal distribution, as well as from those originating in the domains of the facial, glossopharyngeal and vagus nerves. Conversely, equal significance has not been given to the reflection of pain from the aural apparatus to the areas supplied by these cranial nerves. While it has been observed not uncommonly that *acute* inflammatory processes of the middle ear and mastoid are capable of producing pain about the face, the same possibility has not been accorded to the *chronic* forms of otitis media and mastoiditis. With this in mind, HANSEL (*Ann. Otol., Rhinol. and Laryngol.*, 1929, **38**, 335) presented the data of 3 cases to demonstrate that pain can be referred to the second and third divisions of the trigeminal nerve as a result of chronic suppuration of the tympanic cavity and mastoidal cells. After reviewing the embryology, anatomy and neurohistology of the subject, he states that "in the final analysis of the nerve supply of the middle ear, mastoid and contiguous cutaneous area, it is apparent that there are intimate anastomoses between the various nerves involved to such an extent that they all form a nerve plexus." Moreover, several pathways along which these impulses may travel from the otitic structures to the "trigeminal areas" are indicated and their importance evaluated.

Pemphigus Primary in the Larynx.—Pemphigus involving the pharyngeal and oral mucosa primarily or secondarily to its manifestation on the skin is not infrequently seen. Pemphigus restricted to the larynx as a primary lesion for a period of twelve weeks before cutaneous involvement is of most unusual occurrence—even when considering *obscure* laryngeal conditions. In reporting a seemingly clear-cut case of pemphigus presenting early blebs on the epiglottis and right arytenoid, MURPHY (*Arch. Otolaryngol.*, 1929, **10**, 188) by way of differential diagnosis, points out that the laryngeal lesions produce hyperemic spots resembling a superficial angioma in contradistinction to the diphtheroid patches produced by maceration of the denuded areas in the mouth. Inasmuch as the blebs may form and rupture in a few hours, repeated daily examinations should be made in all suspected cases.

Value of Barbital Before Local Anesthesia.—The most efficient agent to effect anesthesia of mucous membranes by topical application is cocain—an admittedly dangerous drug because of its highly poisonous potentialities: In view of the fact that a suitable substitute for cocain—one capable of producing satisfactory anesthesia and at the same time of exerting no untoward systemic effects—is as yet unknown, the rhinolaryngologist has been forced to continue its employment in various operative procedures of the nose and throat. In the absence of an ideal local anesthetic, intensive investigation has been undertaken in the hope of finding some substance which could act as a more successful prophylactic or antidote to that distressing and not infrequently fatal condition—acute cocainism—than such ordinarily used drugs as morphin, atropin and scopolamin. As previously indicated in these columns,[1]

[1] Phenobarbital in the Prophylaxis and Treatment of Acute Cocain Intoxications, AM. J. MED. SCI., 1927, **173**, 441.

experimental and clinical evidence has pointed to the various salts of barbituric as the most promising preparations whereby the toxic action of cocain, and to a lesser degree novocain and others, might be obviated or neutralized. Of these, the popular compounds have been diethyl barbituric acid (barbital) and its sodium salt (sodium barbital), phenyl ethyl barbituric acid (luminal) and n-butyl ethyl barbituric acid (neonal). Interested in this important problem, BARLOW (*Ann. Otol., Rhinol and Laryngol.*, 1929, **38**, 421) reports encouraging clinical results following the oral administration of 5 or 10 grains of sodium barbital or of $1\frac{1}{2}$ grains of neonal, one hour before operation.

RADIOLOGY

UNDER THE CHARGE OF

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Late Effects of Treatment of the Thymus.—A study by BARNES (*Am. J. Roent. and Rad. Therap.*, 1929, **22**, 220) of 63 children who received irradiation treatment of the thymus from three and a half to eight years ago fails to demonstrate any constant deviation from normal, in either the physical or mental spheres, which might be attributed to the treatment, although relatively high dosages were used.

Etiology of the Ill-health of Children Born After Irradiation.—This study represents part of an investigation by MURPHY and GOLDSTEIN (*Am. J. Roent. and Rad. Therap.*, 1929, **22**, 207) in the Institue of Gynecologic Research, University of Pennsylvania. Twenty-four per cent of 650 pregnancies associated with pelvic radium or Roentgen irradiation (preconception or postconception in time) ended in abortion; 13 per cent terminated in the birth of unhealthy children. One out of every 10 or 11 children born after *preconception* pelvic irradiation was unhealthy, whereas one out of every 2 children born after *postconception* irradiation was unhealthy. The ill-health of 24 of the 46 unhealthy children born after *preconception* irradiation was attributed to such influence as the following: (*a*) Six cases of child health disturbances were found to be due to maternal ill-health prior to irradiation or during pregnancy. (*b*) The ill-health of 13 children was believed to have been the result of complications incident to delivery or of prematurity. (*c*) In 3 cases the ill-health was believed to be the result of accidental causes. (*d*) Two unhealthy children later became healthy. The etiology of the ill-health of 22 children could not be determined. In this group there were only 7 seriously defective children. Only one child out of every

59 children born after *preconception* irradiation exhibited some gross anatomic defect of unknown origin. In this small number (one in 59) of defective children the disturbance may have been caused by the previous ovarian irradiation, but it is the belief of the writers that if the irradiation had been the etiologic factor in the production of the condition, the defects would have occurred with greater frequency, regularity, and uniformity. Finally, it cannot be stated with certainty that preconception maternal pelvic irradiation is entirely free from danger to subsequent offspring because of the occurrence of a few defective children born after such treatment.

Radiotherapy for Tumors of the Testis.—DESJARDINS, SQUIRE and MORTON (*Am. J. Roent. and Rad. Therap.*, 1929, **22**, 137) state that Ewing divides testicular tumors into three groups: (1) the relatively benign and slow-growing teratomas composed of highly differentiated tissues arranged to suggest adult organs; (2) an intermediate group including the less differentiated, or teratoid, tumors, and (3) the most common and most malignant tumor of the testis, often miscalled sarcoma, but which he designates as embryonal carcinoma. Of 101 tumors studied by Desjardins and his associates, 69 were embryonal carcinomas (seminomas of Chevassu); 27 were mixed, or teratoid, tumors; 2 were teratomas or testicular dermoids; 2 were sarcomas and 1 had features suggesting chorioma. A comparison of surgery and radiotherapy cannot be made because they are used in different groups of patients. Radiotherapy is employed only after surgery has exhausted its efforts, or when, because the disease is too extensive, surgery cannot be employed. All that can be said for the present is that, in a small number of cases surgical removal of the tumor results in permanent cure; that radiotherapy is a valuable method of treating inoperable cases or cases in which metastasis has occurred in spite of operation, and that the most common tumor of the testis, embryonal carcinoma, is peculiarly and characteristically vulnerable to irradiation, thus providing a means of differentiating such tumors from other newgrowths. The results in embryonal carcinoma are always better and more lasting than in the mixed, or teratoid, tumors. Roentgen or radium rays have little if any influence on true testicular teratoma.

Bronchiectasis.—In about 60 per cent of all cases a diagnosis of bronchiectasis can be made from a study of the plain films, according to HARTUNG (*Am. J. Roent. and Rad. Therap.*, 1929, **22**, 120). Abnormalities of the bronchial wall plus a variable amount of air and secretion in the dilated bronchi produce the Roentgen image associated with bronchiectasis. It is characterized by an increase of the linear markings with small irregular densities, usually occurring in the lower lobes. In the advanced uncomplicated case there is a honeycomb appearance which is almost pathognomonic. In the majority of the remaining 40 per cent the plain films will reveal findings of a nature to indicate the probable presence of bronchiectasis or the desirability of further investigation by bronchography. Diagnostic bronchography with iodized oil is absolutely essential for obtaining accurate information relative to the nature, situation and extent of bronchiectasis.

NEUROLOGY AND PSYCHIATRY

UNDER THE CHARGE OF

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New Vestibular Complexes for Localization of Lesions of the Brain.—FISHER and GLASER (*Arch. Neur. and Psychiat.*, 1929, **21**, 876) present a study of vestibular reactions in 139 cases of brain lesions. They consider that while well-developed spontaneous nystagmus in any direction indicates a pathological condition, only vertical nystagmus is specifically indicative of a pathologic condition of the brain as it does not occur in peripheral lesions. Poor pelvic girdle movements are also suggestive of a brain lesion and there is a disproportion between nystagmus and vertigo after turning. Disproportion in the activity or duration of the responses from the horizontal and vertical canals of the same side after douching, or loss of nystagmus from the vertical canals with past pointing, perverted nystagmus, perversion of direction after stimulation, dissociated movements of the two eyes after stimulation, a loss of all vestibular responses after stimulation with good hearing, and conjugate deviation of the eyes after stimulation instead of the full nystagmus are all suggestive evidence. In all cases presented one or more of the above conditions existed. The nature of the disturbance cannot be determined from such evidence. They consider that former ideas concerning the relationship of such abnormalities to generally increased intracranial pressure must be abandoned because in some cases with markedly increased spinal manometric pressure none of the phenomena were present and in some cases the phenomena were marked when the spinal pressure showed no increase. Since these abnormalities indicate a lesion of the brain not always of a destructive nature he considers them probably due to local pressure. In separating supra- and subtentorial lesions he gives the following criteria: Patients with subtentorial lesions do not become nauseated, vomit or perspire, regardless of the amount of stimulation administered. Patients with supratentorial lesions are frequently quite susceptible, hence increased susceptibility of a patient to stimulation of the ear excludes the presence of a lesion in the posterior fossa but immunity from disturbances does not necessarily place the lesion subtentorially. He calls attention to the fact that normal persons may frequently be upset by stimulation of the ear, "therefore, this phenomenon, appearing during the examination of a patient, does not necessarily indicate the presence of a lesion of the brain, but it does indicate that if a lesion is present it is subtentorial." Susceptibility was particularly marked in lesions of the frontal lobe, the motor area, the temporoparietal area and the pituitary and suprasellar lesions. Susceptibility was absent in patients with

lesions of the temporal lobe, lesions of the occipital lobe and all subtentorial lesions. As to the side involved in cerebral lesions uncertain spontaneous pointing or uncertain past pointing of the arm or leg after stimulation indicates a lesion of the opposite side. Conjugate deviation may be present after stimulation to the side of the lesion. Interference with or absence of all vestibular responses from one ear indicates a lesion of the opposite side. Perversion of the nystagmus from the horizontal semicircular canal indicates a lesion on the same side. By means of these signs he was able to localize correctly as to side, 31 of 33 patients. The other 12 did not have lateralizing signs. In cerebellar lesions the side is indicated by uncertain pointing of the arm or leg on the same side; interference with or loss of all vestibular responses after stimulation on the side of the lesion; impairment of nystagmus from the horizontal semicircular canal on the same side; interference with responses from the vertical semicircular canals on the same side; and deafness on the side of the lesion. Of 6 cases 3 could not be placed as to side, 1 case was wrongly placed and the other 2 were correctly placed. In cases of lesions of the cerebellopontile angle the tumor was always found on the side on which the entire function of the eighth nerve was disturbed. The author then gives diagnostic complexes for each anatomic area and these groups of findings are definite enough to be of some localizing value. He concludes as follows: "A lesion of the brain usually causes abnormal reactions to the vestibular tests. Generalized increased intracranial pressure, as such, cannot be diagnosed by the vestibular tests. The vestibular observations indicative of the laterality of a lesion are definite and reliable, when present, but these signs are not exhibited in all cases of lesion of the brain. The vestibular tests can usually differentiate definitely between a supratentorial and a subtentorial lesion. Each anatomic area presents vestibular group observations of its own. While in the majority of cases the diagnosis of tumors of the brain can be made by the vestibular tests, their value would be the greatest when taken in conjunction with the general clinical observations." (The percentage of accuracy as presented in this study, if corroborated by clinical experience would make these new vestibular complexes extremely valuable adjuncts to our diagnosis of focal lesions.)

The Innervation of the Thymus.—PINES and MAJMAN (*J. Nerv. and Ment. Dis.*, 1929, **69**, 361) present a study of the nerve supply of the thymus gland as found in mice, rabbits, cats and dogs. They find that the nerve bundles all enter the gland, extend through the interstitial tissue ramifying and following the tissue between the lobules. They gradually decrease in size and penetrate by means of thin bundles within the lobular septa of connective tissue. The thin nerve bundles along the vessels detach numerous fibers which form peculiar plexuses about the vascular walls. They differentiate two types of nerve plexuses, one in the adventitia of the vessels and the other within the medial tunic, these latter being the vasomotor nerves. As the vessels decrease in size the large nerve branches disappear and the thick nets become thin pearly threads and are covered with knobs. In the connective tissue between the lobules they find a terminal nerve apparatus of an ovoid or bulblike shape which they consider as a primitive receptive apparatus. The fibers from which they derive are thicker than the

vascular nerve fibers and do not show any varicosity. Certain of the vascular fibers they judge to be of cerebrospinal origin. They penetrate within the gland with the branches of the vagus. The nerve fibers penetrate also into the lobules and are diffusely spread throughout the parenchyma detaching lateral branches and terminal ramifications which end with small knobs adjacent to the cells. They consider those to represent the parenchymal nerve apparatus and to be closely related to the specific function of the gland. Hassal's corpuscles, they find surrounded outwardly by a nerve fiber widening along its limits or by terminal ovoid-like thickenings also adjacent to the inferior part of the tunic. They found no sympathetic ganglion cells. They conclude that the thymus gland is supplied with a thoroughly differentiated nerve apparatus. They find vascular nerves, sympathetic parenchymatous glandular nerve apparatus, and receptor apparatus. The whole innervating apparatus they believe to be partly of sympathetic and partly of cerebrospinal origin. "Thus the analysis of the nerve apparatus of the glands shows that all the elements of the tissue are under nerve control and nothing can occur within the gland without the regulation or registration of the activity by the nervous system." They conceive the receptor nerves as being stimulated by pressure at some stage in the secretory activity of the lymphoid lobules.

PATHOLOGY AND BACTERIOLOGY

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A Case of Periarteritis Nodosa.—GRAY (*J. Path. and Bact.*, 1929, **32**, 787) adds another case description with necropsy findings to the number of about 127 reported cases of periarteritis nodosa. Although no vascular lesions were conspicuous on gross examination of the tissues, histologic inspection of the kidneys, liver, spleen and heart revealed a lesion of the smaller arteries and arterioles. The relatively more acute lesions predominated in the arterioles, where necrosis of the vessel wall, with or without swelling of the intima was surrounded by a cellular infiltration with a preponderance of polymorphonuclear leukocytes. The lesions of longer standing, such as were observed more often in the smaller arteries were characterized by a cellular thickening of the intima, often obliterating the lumen, a partial destruction of muscular and elastic tissue, and a cellular infiltration in and around the wall, the latter being composed in addition to many polymorphonuclear cells of a larger number of plasma and other mononuclear cells as well as fibroblasts, and a higher proportion of eosinophils. A finding of especial interest

in view of the existence of disease in the afferent arterioles and interlobular arteries, was the occurrence of extreme proliferation of endothelium in the glomerular tufts, narrowing most loops, obliterating others, associated with a hyperplasia of the cells of Bowman's capsule, which lead in some instances to the formation of typical crescents. No aneurysmal formations were found in any of the arteries.

Congenital Anomalies of the Liver.—MACMAHON (*Am. J. Path.*, 1929, **5**, 499) reviews several cases. Many of the more common types are described and explained on an embryologic basis. The anomalies may be divided into two groups, in the first of which a retardation of development has occurred so that the liver or a part of it in the full term child resembles that of a developing fetus. The second group includes those cases of true developmental anomalies in which either the parenchyma or the connective tissue of the portal areas is involved. One type that is characterized by increase in number and dilatation of the periportal bile ducts, with an accompanying increase in the portal connective tissue may persist throughout life. With this anomaly is associated the congenital cyst of liver and frequently bilateral congenital cystic kidneys.

Allergic Inflammation in Kidneys.—HEPLER and SIMONDS (*Am. J. Path.*, 1929, **5**, 473) produced allergic inflammation in the kidneys of rabbits previously sensitized subcutaneously to foreign proteins. The reaction produced was very rapid in occurrence and intense, an advanced acute inflammatory reaction with hemorrhage and early necrosis being present in twenty-four hours. Hemorrhage was found in all the injected kidneys when autopsied within seventy-two hours. The exudate was chiefly leukocytic with relatively little fluid. The necrosis was probably due to the direct toxic effect of the antigen on the sensitized tissue, it being absent about the hemorrhage in the nonsensitized rabbits.

Immune Cellular Reactions in Experimental Acute Peritonitis.—STEINBERG and SNYDER (*Arch. Path.*, 1929, **8**, 419) experimenting with dogs, some of which had been previously immunized to Bacillus coli, found that in the first twenty-four hours following the production of fecal peritonitis the cellular reaction was predominantly polymorphonuclear. Bacteria in the peritoneal cavity were almost completely phagocyted in the immune animals at the end of eight hours. The action of the polymorphonuclear leukocytes in immune dogs was not specific, since they phagocyted other organisms as well as Bacillus coli. The difference in the cellular reaction of immune and nonimmune animals, they found to be quantitative. The immune dogs mobilized polymorphonuclears more rapidly and in far greater number than did the nonimmune.

Traumatic (False) Aneurysm of the Aorta.—Traumatic rupture with subsequent false aneurysm formation of the aorta is perhaps most apt to occur in the regions of relative fixation, two finger-breadths above the semilunar cusps and at the level of insertion of the ductus arteriosus. SHENNAN (*J. Path. and Bact.*, 1929, **32**, 795) reports a case of traumatic

aneurysm below the latter region at the level of origin of the fifth pair of intercostal arteries, occurring in a man, aged fifty-seven years. The patient, who had been knocked over by a bicycle, presumably falling on his chest and shoulder, lived for eight weeks to die of rupture of the aneurysm into the esophagus. The aortic arch presented a small amount of atheroma. Between the fourth and sixth aortic intercostals an irregular opening existing in the posterior wall, measuring 3 cm. transversely and 1.2 cm. from above downward, led into a cavity lined with irregular antemortem thrombus opening into the esophagus. Microscopic examination of the wall of the aorta at a short distance from the aneurysm showed evidence of hyaline and fatty degeneration with calcareous deposits.

Typical Lesions Produced in Animals by a Strain of Sporothrix Found in Well Water.—CATANEI (*Comp. rend. Soc. de biol.*, 1929, **101**, 447), with a strain of sporothrix found in well water, and which differed morphologically from the Sporothrix beurmanni, was able to produce experimental lesions in guinea pigs, mice and in a monkey, which were sometimes fatal and showed the anatomic pathologic characters analogous to those in the lesions of human sporotrichosis.

Growth of Bacillus Tetani in Suspensions of Agar.—Agar is so commonly used in bacteriologic media in a relatively high amount that little attention has been paid to its use in relatively small quantities. BELIN (*Comp. rend. Soc. de biol.*, 1929, **101**, 435) declares that 0.1 per cent agar makes a suspension exactly intermediate between a solid and a liquid media and favors very considerably the growth of Bacillus tetani.

Late Gross Lesions in the Aorta and Pulmonary Artery Following Rheumatic Fever.—GRAY and AITKEN (*Arch. Path.*, 1929, **8**, 451) present 4 cases of rheumatic fever in which gross lesions, believed to be of rheumatic origin, were found in the aorta and pulmonary artery. One case showed false aneurysm of aorta. Each case had a clinical history of one or more attacks of rheumatic fever or of chorea or of repeated attacks of tonsillitis. Each had typical rheumatic lesions in the heart and the possibility of syphilis was ruled out by absence of any evidence of it in the history, serologic reaction or in the gross or microscopic appearance of the aorta and other organs. The gross lesions of aorta consisted of a fine stippling of the intima sufficiently marked in one case to give a honey-comb appearance. The intima and adventitia in these areas were thickened and the media markedly thinned. The authors emphasize an eccentric fibrosis of the veins as being rheumatic. Gross scars observed in two cases were believed to be due to thrombosis of vasa vasorum in the course of a rheumatic process. The aneurysm described is also explained on a rheumatic basis. It is partly of dissecting type and partly false. The dissection had split the media. The intima and adventitia were markedly thickened but the intima except for the opening into the aneurysm was smooth and showed no gross lesion.

HYGIENE AND PUBLIC HEALTH

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The Effect of Sun and Air and Air Baths on the Respiratory Gaseous Exchange in Man.—JAKOWENKO (*Am. J. Hyg.*, 1929, **10**, 165) states that the respiratory metabolism, determined in an individual after a fast of twelve hours and after an hour's rest in bed in a health resort, is in the majority of cases increased on comparison with Harris-Benedict's normal figures. The conditions and the life in a health resort (light clothes, air and sun baths, sea bathing, emotions) are as a rule sufficient to produce an increase of the metabolism in the majority of people. However, there are some whose respiratory exchange does not rise in similar surroundings above Harris-Benedict's figures. During air and sun baths and during air baths the gaseous exchange in man tends to show a further increase. In certain conditions this metabolism may decrease below the level of basal metabolism, which had been observed in the same person before the bath. The height of the respiratory gaseous exchange in man during air and sun baths and air baths depends among others on the combination of meteorologic conditions, either producing a relatively strong cooling of the human body or favoring an increase of heat in it; these factors are: temperature, humidity, air movement and the intensity of solar and skylight radiation. Among all the climatic factors which favor the cooling of the body and the increase of gaseous exchange in man during air baths on the beach, the rate of air movement is of the greatest importance. Besides these external factors, there are also internal constitutional factors, which determine the amplitude of fluctuations shown by the gaseous exchange of man at the health resort. All the climatic factors may be divided into 2 groups according to their effect on the gaseous exchange in man: (1) Those increasing the gaseous exchange, apparently due to the irritation of the peripheral cutaneous nerve endings of the sympathetic nervous system, such as low temperature and air movement, and (2) those factors which decrease the gaseous exchange (high air-temperature, absence of air movement and excess of heat produced by solar radiation). The writer believes that a moderate increase in the gaseous exchange of man should be the purpose of climatic treatment. The latter proves to be beneficial to a diseased and exhausted body, due to its production of an increased activity of specific vegetative organs (the liver, the heart, and so forth), that of the endocrinous system and of the oxidating processes in the tissues.

Preparalytic Poliomyelitis. Further Observations on Treatment with Convalescent Serum.—AYCOCK and others (*J. Infect. Dis.*, 1929, **45**, 175) treated 116 cases of preparalytic poliomyelitis with human convalescent serum. The outcome of these cases as measured by case fatality rate, percentage of cases which developed no paralysis, percentage of cases which developed paralysis of the two severe grades, as well as by the average amount of paralysis per case was strikingly different from the outcome of untreated cases in the same outbreak. That this difference was not due in any great degree to the inclusion among the treated cases by reason of early diagnosis of milder forms of the disease, which are ordinarily missed, was indicated by the close correspondence between the results in the state at large and in Watertown-Waltham, where there were increased opportunities for detecting milder forms of the disease and where a larger portion of all cases was seen and treated. A relatively enormous number of missed cases must be assumed to have occurred in order to equalize the outcome of treated and untreated cases. A house to house canvass in one locality where the disease was prevalent failed to disclose the occurrence of any number of missed cases. All treated cases presented typical signs and symptoms of preparalytic poliomyelitis. The subsequent occurrence of some paralysis in 61.2 per cent of the treated cases indicated that a nonparalytic form of the disease was not being dealt with. Twenty-three per cent of the cases which developed no paralysis were of the so-called dromedary type as compared with 26.8 per cent of the cases which did develop paralysis. Since the dromedary phenomenon is peculiar to poliomyelitis, this is regarded as an additional substantiation of the diagnosis in the group of cases in which no paralysis developed. Of the 143 patients seen as suspected preparalytic poliomyelitis, who were excluded, the majority subsequently were found to be suffering from other conditions. In only 8 cases could the suggestion of abortive (not preparalytic) poliomyelitis be considered.

Sinusitis and Otitis in Swimmers.—SAUNDERS (*Am. J. Hyg.*, 1929, **10**, 253) states that the value of swimming as a means of exercise more than compensates for its dangers for the normal individual. Furthermore, the dangers can be greatly lessened. Matters that especially require attention are means of reducing trauma to the nose and ears and correct habits of breathing. Accordingly, methods of plugging the nose are worth attention. In high and fancy diving this is useful. The use of an oil spray in the nose before entering the water has been suggested by Skillern and others. This helpful measure is almost universally neglected. Persons with narrow nasal passages, deviated septums and other anatomic abnormalities are much more prone to infection than those who have unobstructed sinus drainage. This leads to the suggestion that all persons wishing to do diving and polo first have a nasal examination, with subsequent medical or surgical treatment if indicated. To these local measures of reducing trauma and consequently the likelihood of bacterial invasion should be added the general measure of supervision of the length of the swimming period. Forty-five minutes in the water is probably long enough. There is evidence that bodily resistance is reduced with exposures longer than this. Correct habits of breathing are of major importance. Breathing in

swimming is just the reverse of that in any other activity. Inhalation is always through the mouth while exhalation should be done through both the nose and mouth simultaneously. The latter is difficult but is well worth learning. It is impossible to exhale with sufficient rapidity through the nose and if the mouth is used exclusively water flows into the nasal passages.

Streptococci From Cases of Epidemic Septic Sore Throat, Scarlet Fever and Erysipelas.—WHEELER (*J. Prev. Med.*, 1930, **4**, 1) studied the cultural, biochemical and serological reactions of hemolytic streptococci isolated from outbreaks of septic sore throat in Wayland and Savannah, N. Y. In the Savannah outbreak, the streptococci isolated from patients and from milk from the infected udder of a cow supplying milk to these persons were found to be identical in all respects. The majority of the strains isolated from both of these epidemics gave the cultural and biochemical reactions of "Streptococcus epidemicus." The study of the toxin production and agglutination reactions of streptococci isolated from these two epidemics and from two other outbreaks of epidemic septic sore throat, as well as the demonstration of well-defined capsules on streptococci isolated from typical cases of scarlet fever and erysipelas, indicate that the streptococci associated with epidemic septic sore throat, scarlet fever and erysipelas cannot, by any method now available, be separated into specific groups.

PHYSIOLOGY

PROCEEDINGS OF

THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA

SESSION OF FEBRUARY 17, 1930.

Alteration in Response to Insulin During Experimental Leukocytosis.—ISOLDE T. ZECKWER (from the Department of Pathology, University of Pennsylvania). The purpose of the experiments was to learn what factors are involved in the altered response to insulin which may be observed during acute infections in diabetic patients. For the present, the experiments were limited to a study of the effect of leukocytosis induced by a chemical rather than a bacterial irritant, in normal rabbits.

Each of 8 rabbits, under standard conditions, was injected on several occasions with a small convulsive dose of insulin. Then an intense leukocytosis was induced by intravenous injection of 0.1 gm. sodium nucleinate. In 5 rabbits during the period of leukocytosis, at about eighteen hours after injection of the nucleinate, the previously convulsive dose of insulin no longer induced convulsions. These rabbits were allowed to return to normal conditions, when the same dose again caused convulsions. On again inducing leukocytosis by nucleinate, convulsions were again inhibited.

When sodium nucleinate is repeatedly injected the bone marrow becomes exhausted of its myeloid elements, so that a rise in circulating leukocytes no longer occurs. When rabbits which had previously showed insulin inhibition during leukocytosis were brought to the stage where sodium nucleinate no longer caused leukocytosis, convulsions again occurred, when the same dose of insulin was given, as though no nucleinate had been injected. This would appear to indicate that inhibition of insulin action had occurred because of leukocytosis. The blood sugar just before the insulin was injected was within the normal range in the rabbits so far described.

In 3 rabbits no inhibition of insulin action occurred during nucleinate leukocytosis, but in these rabbits the blood sugar was low just before the injection of insulin, about eighteen hours after the injection of the nucleinate.

In the intact rabbit sodium nucleinate injected intravenously caused an abrupt rise in blood sugar, with a maximum at about one hour, followed by a fall to normal or slightly below. The rise did not occur if, some time previous to the injection, one adrenal was excised and the opposite splanchnic nerve cut. Insulin inhibition could be induced during nucleinate leukocytosis in 2 rabbits in which glycogenolysis was prevented by such an operation.

Since insulin is inactivated *in vitro* by the enzymes of leukocytes, it is considered probable that the insulin inhibition during nucleinate leukocytosis is dependent upon the enzymes of the circulating leukocytes.

Penetration of Antibodies into the Central Nervous System of Rabbits.—Jules Freund (from the Henry Phipps Institute, University of Pennsylvania). In passively immunized rabbits antibodies (agglutinins against typhoid bacilli) penetrate into the cerebrospinal fluid even in the absence of inflammation of the meninges. The penetration proceeds slowly; it is finished only several hours after the injection of immune serum. When the penetration is completed the ratio of the titer of serum to that of the cerebrospinal fluid is equal to 100 to 0.3.

The accumulation of antibodies in the brain and spinal cord is finished within fifteen minutes. The ratio of the titer of the serum to those of the extracts of these organs is similar, that is, about 100 to 0.7 (1 cc. of serum compared with extract prepared from 1 gm. of organ). The antibodies cannot be removed from the brain by perfusion.

When antibodies are injected into the cisterna magna, they penetrate into the blood at once, but they remain in the cerebrospinal fluid in excess for one day. Three days after the injection the ratio of the antibody titer of the serum to that of the cerebrospinal fluid is about the same as in rabbits immunized by the venous route. (See previous papers of this series in *Journal of Immunology*, 1927, 1928, 1929.)

Progress in the Characterization of Antibody Action.—S. Mudd, B. Lucké, M. McCutcheon and M. Strumia (from the Henry Phipps Institute and the Department of Pathology, University of Pennsylvania). We have undertaken analysis of the mechanism by which blood serum promotes the phagocytosis of bacteria or other foreign particles. Methods have been developed in these laboratories and elsewhere by

which the properties of bacterial surfaces can be studied directly and the changes effected in them by contact with serum can be ascertained. A quantitative technique for the study of phagocytosis *in vitro* has been developed, using the improved apparatus of O. H. Robertson. Study of the bacterial surfaces and of phagocytosis has been conducted simultaneously upon the same combination of bacteria and serum.

Sera which promote phagocytosis of bacteria have been found invariably to cause certain definite changes in the surface properties of the bacteria, namely increased cohesiveness, decreased surface potential difference and increased resistance to wetting by oil. Similarly, but with certain exceptions, sera which cause these characteristic changes in the bacterial surfaces also promote phagocytosis. The phagocytosis-promoting, agglutinating and surface effects are in quantitative correspondence. A similar striking correspondence has been found between the agglutinating, surface and phagocytosis-promoting effects caused by the euglobulin and pseudoglobulin fractions of antibacterial sera.

Following the technique of F. S. Jones, collodion particles have been coated with precipitinogen and then treated with homologous precipitin sera and their protein fractions. The same sera and serum fractions cause specific precipitation, agglutination or phagocytosis according to the conditions under which they are allowed to react with antigen.

Agglutinating, surface and phagocytosis-promoting effects have thus been found to be quantitatively parallel. This quantitative correspondence of the several effects of a serum or serum globulin fraction has been found both for antibacterial and for antiprotein sera and their globulin fractions. All of the effects are consequences of the deposit of sensitizing serum substances on the antigen surface. The surface deposit so produced by maximal sensitization has similar properties, whether deposited upon acid-fast bacteria or upon precipitinogen-coated collodion particles, that is, the sensitized surface has wetting properties characteristic of protein, is cohesive, and has an isoelectric point between pH 5.5 and 5.8. These are the properties also found for specific precipitate.

These studies thus bring evidence of a new sort in support of the following simple generalization: The combination of antigen and antibody is determined by specific chemical affinities. The effects following this combination, namely precipitation, agglutination, changes in surface properties and phagocytosis, are consequences of the properties primarily of the antibody-protein combined with and deposited upon the antigen surface.

Fixation of Iron by an Inflammatory Reaction.—Valy Menkin (from the Henry Phipps Institute, University of Pennsylvania). It has recently been demonstrated by the writer that a vital dye such as trypan blue when injected intravenously rapidly accumulates in an inflamed area and is fixed there so that the dye fails to reach the draining regional lymphatic nodes. Subsequent quantitative work showed that the rapid accumulation of dyes in inflamed areas is the result of increased capillary permeability with inflammation.

Having established this principle with a dye, further studies were then undertaken to see whether a metal would be fixed *in situ* by the inflammatory reaction. Iron was selected because of the ease of detect-

ing this metal qualitatively in tissues by the Prussian blue reaction. Colloidal iron or ferric chlorid when injected into the normal peritoneal cavity of rabbits rapidly accumulates in the retrosternal lymph nodes as evidence by the Prussian blue reaction. When, however, this metal is injected into an inflamed peritoneal cavity caused either by aleuronat or Staphylococcus aureus, the iron is fixed *in situ* and fails to reach the retrosternal lymph nodes. Quantitative studies of iron content of these lymph nodes in animals injected intraperitoneally with ferric chlorid reveal 56.7 per cent more metal in the nodes of animals with normal peritoneal cavity than in those with inflamed peritoneal cavity.

Experiments were then performed to demonstrate the accumulation of the metal in inflamed areas when ferric chlorid is injected into the circulating blood stream. Acute inflammatory reactions of six to seven hours' duration were obtained by the injection of Staphylococcus aureus into the dermis of the abdomen of rabbits. Such acute inflamed areas do not give the Prussian blue reaction *per se*, but when ferric chlorid is injected intravenously the metal accumulates in these areas and becomes demonstrable by the qualitative test. Quantitative determinations of iron content of inflamed areas of animals that received no iron show as an average figure 9.7 mg. per 100 gm. of dry tissue as compared with 16.2 mg. in animals injected intravenously with ferric chlorid. There is, therefore, in inflamed areas an increase of 67 per cent in the iron content by the intravenous injection of the ferric salt. The average iron content of normal skin areas in injected animals is 10.4 mg. as compared with 8.4 mg. in noninjected animals. This shows an increase in normal skin of 23.8 per cent by the injection of the metal. Hence there is about three times more metal accumulating in inflamed than in normal skin areas. These findings show that iron, like trypan blue, accumulates in an inflamed area when injected intravenously and is fixed there by the inflammatory reaction.

These studies may have clinical applications. It is conceivable that by the accumulation of dye, iron-containing, or other substances in an inflamed area, the character or course of development of the inflammatory reaction may be altered.

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